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FDA PUBLIC WORKSHOP

DEVELOPMENT OF INHALED ANTIBACTERIAL TREATMENTS FOR CYSTIC FIBROSIS AND NON-CYSTIC FIBROSIS BRONCHIECTASIS

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PROCEEDINGS

INTRODUCTORY REMARKS AND PANEL INTRODUCTION

DR. COX: Great. Thanks. So I'm Ed Cox, director of the Office of Antimicrobial Products, and I'm going to start out by welcoming everybody to today's workshop on Developing Therapies for Treatment of Cystic Fibrosis and Nasally Inhaled Antibiotics for the Treatment of Cystic Fibrosis and also Non-CF Bronchiectasis.

And I want to thank folks -- the folks that have come here in person, and I also I know there's a lot of folks that are joining online too.

And, you know, folks that follow area are aware that there have been a number of development programs that have happened over the last several years and I think we've learned some, but we've also encountered some of the challenges of developing therapies in this area.

So we thought given the experiences to-date, it will be a good chance to gather folks together to talk about trial design, to talk about endpoints, to talk about ways that we can overcome some of the

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challenges that we encounter in developing drugs for CF and also for non-CF bronchiectasis.

So we really look forward to an open discussion today. We've got a series of panels. And we'll start out first by talking about some of the device-related issues, then we'll move and talk some about drug development for CF, and then non-CF bronchiectasis will follow in a subsequent panel. So we look forward to an open discussion.

And, you know, these workshops are valuable to us because of your all willingness to come and join us, you know, having your expertise from your various different experiences and disciplines from which you come. And contributing that to the discussion of the meeting really helps a lot as we try and develop ways to facilitate the development of drugs.

And if we think about this, what this is really all about, is really about getting therapies out there to help patients. And I think that's everybody's shared goal and, you know, that's the key thing to keep in mind as we're working through the day.

And I think at this point what we'll do is

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we'll start out by introducing the panelists and what we'll try and do is go around. And one other thing too I should say, lunch -- you can order lunch out there. I think it's just beyond the first conference room. There's a little window there. And they've asked that people who want to get lunch here through their services do so -- put their order in by the break time if you will.

And let's see. Now, I'd like to have the panelists go around and introduce themselves, and I think we'll start with Mr. Hawkins. And just folks know, in the agenda in the back is a list of conflicts of interests and declaration of conflicts of interests. So that's available both in the paper form and on the web.

So we'll ask folks to go around the table. We'll start with Mr. Hawkins. We'll work our way around. And I would ask that folks, you know, state their name and their affiliation. Mr. Hawkins?

MR. HAWKINS: Hi. I'm Chip Hawkins. I'm a cystic fibrosis patient, and as a CF patient, I use a lot of the drugs that are in development or are

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available now. But I'm also -- I also take part in a good number of drug trials. I've been in 15 or 20 or so. So hopefully I have some perspective to add to this meeting from both the patient and participant part of the equation.

DR. FROEHLICH: And I'm Juergen Froehlich, chief medical officer at Aradigm. I have been quite heavily involved in Phase III development for ciprofloxacin DI.

DR. CHALMERS: My name is James Chalmers. I'm a respiratory physician from the University of Dundee in the U.K. and I also chair the European Bronchiectasis Network.

DR. BARKER: I'm Alan Barker from Portland, Oregon at the Oregon Health & Science University. I've been involved in clinical research in bronchiectasis for a number of years.

DR. NOONE: Peadar Noone. I'm at the University of North Carolina in Chapel Hill and I've been involved in CF care and non-CF antimycobacterial treatment for several years.

DR. HAMBLETT: Nicole Hamblett, professor of

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biostatistics and pediatrics at the University of Washington. I also co-direct the CF Therapeutics Development Network coordinating center at Seattle Children's Hospital.

DR. TRACY: LaRee Tracy. My background is in statistics and epidemiology. I'm here at FDA in the Office of Biostatistics. And I was the statistical reviewer on the Aradigm ciprofloxacin product review.

DR. VANDEVANTER: Dutch VanDevanter. I'm an adjunct professor of pediatrics at Case Western Reserve University. I've been in CF trial design and analysis for about 20 years. And I'm here representing Horizon Pharma.

DR. KIM: Peter Kim, clinical team leader, Division of Anti-Infective Products, FDA.

DR. AKSAMIT: Tim Aksamit, Mayo Clinic, Rochester, Minnesota. I'm a respiratory physician and involved in bronchiectasis and NTM and currently chair of the U.S. Bronchiectasis and NTM Registry.

DR. KADOORIE. I'm Chris Kadoorie. I'm a statistical reviewer here at FDA and I've had some, you know, experience with both non-CF and CF submissions

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and presented it at several AC meeting.

DR. TINO: Good morning. I'm Greg Tino. I'm a pulmonary and a critical care physician at the University of Pennsylvania and I've had longstanding both clinical and research interest in bronchiectasis. And I'm the principal investigator at Penn of the Bronchiectasis Research Registry of the United States.

DR. FLUME: And I'm Patrick Flume at the Medical University of South Carolina in Charleston. I'm the CF center director there, but also have large programs in both bronchiectasis and NTM.

DR. NAMBIAR: Good morning. I'm Sumathi Nambiar, director, Division of Anti-Infective Products, CDER, FDA.

DR. SMITH: Good morning. I'm Thomas Smith, the clinical team leader in the Division of Anti-Infective Products, FDA.

DR. NICHOLS: Dave Nichols, University of Washington. I'm a CF provider and the medical director of the TDN Coordinating Center.

DR. ZEITLIN: I'm Pam Zeitlin, chair of Pediatrics at National Jewish Health and I have

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participated in CF clinical trials over many years, even with Mr. Hawkins.

DR. ALDER: Good morning. I'm Jeff Alder, founder of Anti-Infective Consulting. And about seven months ago, I was the lead presenter for Bayer for their Cipro DPI at the Advisory Committee as they tried to gain approval.

DR. ELLENBERG: Susan Ellenberg, professor of Biostatistics at the University of Pennsylvania School of Medicine, with general expertise on clinical trials.

DR. ALLENDE: Maria Allende. I'm a medical officer in the Division of Anti-Infective Products and I have been the reviewer of inhaled therapies in the last Advisory Committee meeting.

DR. LIM: I'm Bob Lim. I'm clinical team leader, Division of Pulmonary, Allergy and Rheumatology Products, FDA.

DR. FOLLMANN: I'm Dean Follmann, head of Biostatistics at the National Institute of Allergy and Infectious Diseases.

DR. MISHRA: Hi. I'm Shrimant Mishra and I'm the medical officer in the Division of Anti-Infected

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Products.

DR. DHAND: I'm Rajiv Dhand. I'm an adult pulmonary and critical care physician at the University of Tennessee in Knoxville. I've had a longstanding interest in aerosolized therapies, including inhaled antibiotics.

DR. LAKHANI: Good morning. I'm Deepika Lakhani. I'm with the Respiratory Devices branch in the Center for Devices.

MR. ZIMMERMAN: I'm Jasan Zimmerman. I'm the non-CF bronchiectasis patient representative. I participated on the Advisory Council for the Bayer and the Aradigm submissions.

DR. CHEN: I'm Wen-Hung Chen. I'm the team leader of the Clinical Outcome Assessment Staff at the Office of New Drugs in CDER.

DR. COX: Great. Thank you all. So at this point what we'll do is we'll move to the first talk, and the first talk deals with some of the cost cutting issues that deal with devices that are used to essentially inhale antimicrobial agents.

So we'll start out with Quynh Nguyen and Quynh

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joins us from CDRH and we're grateful that -- did I get that right?

DR. NGUYEN: (off mic)

DR. COX: CDER. Oh, you're a device person from CDER. Our CDRH person will follow with the second half of the talk. And we're glad that Quynh was able to join us, because devices issues are certainly something that we deal with in dealing with these products. So, Quynh, thank you.

CROSS-CUTTING DEVICE AND HUMAN FACTORS CHALLENGES AND CONSIDERATIONS

DR. NGUYEN: Good morning. My name is Quynh Nguyen. I'm the associate director for Human Factors with the Division of Medication Error Prevention and Analysis. I'm pleased to be here to talk about CDER's perspective in the role of human factors for inhalation products design and development.

So in the next slide we'll show the disclaimer, which was produced by government employees, are freely reproduced and any product provided as examples are for illustrative purposes only.

Next slide please. So let's first off start

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defining medication error, what is a medication error? A medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the hands of the healthcare provider, patient or consumer.

So the figure on the right -- if you can just go back please -- shows that while there are some medication errors that may result in no harm and some drug adverse events may result in non-preventable harm, there's the intersection, as you can see in the middle, where medication errors and adverse drug events intersect and that's where there's preventable harm.

Next please. Then what is human factors? So human factors is a scientific discipline that's designed to evaluate the understanding of interactions among human and elements of the system in order to optimize human wellbeing and overall performance.

Next please. So human factors is really at the core of medication error prevention. As we can better understand how users interact with the system, we can better prevent medication errors and therefore optimize human wellbeing.

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Next please. So who looks at medication errors? So it's the Division of Medication Error Prevention and Analysis. We were created in 1999. We're comprised of scientists and healthcare professionals with varying backgrounds. We have a total of 53 employees. We are aligned by Office of New Drugs therapeutic areas. And we lead the CDER's review pertaining to medication error prevention and analysis as well as human factors for drug and therapeutic biologics.

Next please. This is where we sit in the Center for Drug Evaluation and Research. We are in the Office of f Medication Error and Prevention and Risk Management, which is under the Office of Surveillance and Epidemiology.

Next please. Our mission is to increase safe use of drug products by minimizing use errors that are related to product design, naming, labeling and packaging.

Next please. To achieve our mission, we are involved in all of the following. So we perform assessments of proprietary names and we serve as

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signatory for these reviews. We also perform labels, labeling, packaging and product design to ensure safe medication use. We also perform human factors evaluations to ensure that the product is optimized and ready for safe and effective use. We perform post-market surveillance to identify safety signal and take appropriate action as necessary. We also participate in guidance development for FDA and industry. In addition, we participate in work groups and advisory committees.

Next please. So next I like to show a video. So unfortunately, we are unable to play the video, but you do have the links. So when you get a chance, you can take a look at the video. It's a very interesting video that illustrates -- yeah, we can try.

(video playing)

DR. NGUYEN: So as you can see from this video, it illustrates the concept that users can use a product in unexpected ways and the idea is to make sure that we anticipate these usages as they occur and prevent it from happening when the product gets in the market. And in this particular instance, the product

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is in the hands of the patient and the patient did commit a medication error.

Which brings me to the next set of considerations with regards to reactive and proactive approaches. Thank you. So historically some design issues with drug products were not identified and remedy until post-marketing, and in some cases, some of these medication errors have already reached and harmed the patients.

Today our approach is more proactive, where we identify design issues proactively and address those issues prior to marketing of the product to prevent some medication errors from occurring.

So that proactive approach also applies to our evaluations of combination products, where inhalation products fall under. Here I provide a formal definition for combination products, which you all are familiar with. So combination products are therapeutic and diagnostic products that combine more than one constituent that's regulated by the FDA. It can combine either a drug and a biologic, a drug and a device or a drug and a biologic.

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And combination products can be physically combined, for example, an auto-injector, or chemically combined. They can also be co-packaged in a kit, for example, a vial that's co-packaged in a prefilled syringe. Or they can be separate and cross-labeled products, for example, a specific drug product that's intended for inhalation that specifies the need to use that product with a specific device constituent.

Here's some examples of combination products for which you are familiar with, prefilled syringes, pen-injectors, auto-injectors, inhalation products, transdermal patches, drug infusion devices, kits containing drug administration devices.

So with respect to combination products and the FDA's regulatory authority, it stems from device regulation, which is 21 CFR 820.30, which specifies the requirement for the device manufacturer to evaluate use-related hazards and to validate the user interface. It also stems from a drug regulation which is from the Food, Drug, and Cosmetic Act, which specifies the need to reduce medication errors through improved product design. In addition, we also have PDUFA goal, which

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specifies the need to minimize use-related hazards.

So human factor studies may be needed to demonstrate the elimination or minimization of use-related hazards and medication errors. And the key term here is "may be". So we don't always ask for human factors for combination products, in particular inhalation products. The determination on the human factors data need is based on the use-related hazards.

So let me walk through the process in terms of how human factors engineering can be used to optimize the product. So, for example, a high-risk product where you may start with the original design, and when you apply the human factors engineering process, the idea is to ensure that the product is more optimized and that the design has been designed in a manner that allows for safe and effective use. And the same principles apply for a low-risk product as well.

So let me walk through the human factors engineering process. First, we define the intended users, use environments and user interface. So for inhalation products the intended users may be patients and caregivers using the product at home or healthcare

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providers using the product in a healthcare setting. The use environments, as I mentioned, it can be at home or a healthcare setting. And the user interface is of course the device constituent of the product.

And next we identify use-related hazards. So this step allows us to understand what potential hazards could occur when a user is using the product and allow us to understand what critical tests are needed to be performed and evaluated. Then we evaluate and implement risk mitigation control measures. And then we conduct a human factors simulated-use validation study to demonstrate safe and effective use.

Within this human factors validation study, we can identify and conclude the use-related risks are acceptable and/or new use-related hazards are not introduced. If the conclusion is yes to both of those questions, then we can go ahead and document the process. Now, if the answer is no to either one of those questions, then we need to go back to the step of implementing additional risk control measures and follow the next steps in the flowchart.

Just a few notes on the simulated-use, human

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factors validation testing. The idea is to ensure that the testing is sufficiently realistic so that the results can be generalizable to actual use. In addition, test participants should be given the opportunity to use the product as independently and naturally as possible. Furthermore, if users have access to the product labeling, that product labeling should be provided during the testing. However, the participants can choose to use the product labeling when they need to, but they shouldn't be required to review the product labeling.

This slide shows the drug development process and where human factors engineering process fit in as well as where DMEPA can be involved. So DMEPA can be involved when the IND is filed, but we can be involved as early as the pre-IND phase. And the human factors engineering process should begin from preclinical testing and is carried through Phase IV and the risk analysis is continually updated based on the human factors evaluation and testing.

This is more of a reference slide, where I show specific guidance that mentions considerations for

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human factors for different regulatory pathways. For example, for a new drug the regulatory pathways can be 505(b)(1), 505(b)(2), 351(a) and the applications types can be NDAs or BLAs. And in this space, we do have a draft guidance that was released in February 2016 that's titled Human Factors Studies and Related Clinical Study Considerations for Combination Product Design and Development.

In the generic product space, the regulatory pathway can be 505(j) and the application type is ANDA. And we do have a draft guidance that was released in January of 2017 that's titled Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA.

In the biosimilar space, the regulatory pathway is 351(k) and the application type is BLA. And in this space the same guidance that's applicable for a new drug can be used here.

Now, in the interchangeable space, which is 351(k)(4) and the application type is BLA, we do have a draft guidance that was released in 2017 that provides considerations for demonstrating interchangeability

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with a reference product.

The next few slides provides the FDA release of guidance in terms of timeline for the last 17 years starting with 2000 and it goes through 2017. So I provided these for your reference. You can take a look when you have the time.

And I just like to conclude that ultimately FDA and industry are working collaboratively together to ensure that the outcome for the patient is safe and effective use of medical products.

DR. NAMBIAR: Thanks, Quynh. Are there any clarifying questions for Quynh? Thank you very much, Quynh. So our next speaker would be Deepika Lakhani. She's a team lead in the Respiratory and Pulmonary Devices Branch in the Office of Drug Evaluation -- sorry, Office of Device Evaluation, Center for Devices and Radiologic Health. And the Division of Anti-Infective Products works closely with Deepika and her team when we review applications for inhale therapies. Welcome Deepika.

DR. LAKHANI: Good morning. Thank you for the introduction. I'll jump right in. The outline today

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for the next 15 minutes of my talk is I would go over how we classify medical devices, the respiratory products, with a specific focus on drug device development; the device review considerations for orally inhaled drug products; I'll present a brief case study wherein we collaborated with a sponsor to guide the regulatory development of their product; and have in the end some conclusions.

So from a regulatory standpoint, we divide medical devices into Class I and Class II and Class III. Class I are followed by general controls. They are exempt from any premarket clearance and they are very simple devices, for example, surgical gloves.

Class II are general controls and special controls, where most of these are devices that are involved with products that we are discussing today would be. They mostly require 510(k) if they are for general use and that would be like a nebulizer.

Class III are the highest risk devices that require general controls and premarket approval. They are more of implanted -- permanently implanted devices. So they require extensive review before they can be

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introduced to the patient.

The guidance here in front of us is regarding the 510(k) program that we follow at the CDRH to help the industry decide what is required or whether a device is suitable for a 510(k) and what kind of data needs to be submitted before a 510(k) can be cleared by the FDA.

As Quynh also mentioned, combination products fall under the definition of the 21 CFR 3.2(e) and it's more than one regulated component. It could be a drug and a device like most of the inhaled products are. It could be a biologic and a device or a combination of all three.

Because we are separate entities within the FDA, different centers work closely and collaboratively depending on the product to review such combination products. In case the sponsor is unsure where their product actually falls or who would be the lead center, there is a mechanism available on the FDA website that talks about how to write a request for designation that can help the sponsor to proceed with actually understanding where their device or their product can

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fall into and which center would be involved with the review of that product.

So jumping into the inhalation devices that we see for orally inhaled drug product, we have the general indications or the drug specific indications nebulizers. The general indications nebulizers that I would follow on the next slide are cleared typically via the 510(k) pathway. The drug specific nebulizers, as we see in most of our NDAs relevant to the talk today, are approved typically via the NDA. There are of course the inhalers like the pressurized metered-dose inhalers, dry power inhalers, they are almost always drug specific and they are specifically approved via new drug applications.

So what is a general use inhalation device? Examples of the drug classes that we consider for general use are beta-agonist bronchodilators like albuterol, anticholinergic bronchodilators like ipratropium or anti-inflammatory drugs like cromolyn sodium. Anything that falls outside of such general use is considered a drug specific indication.

The general use indications are cleared by the

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510(k) pathway. And when we come -- there's a database available to understand what has been cleared in the past. All you need to do is put in a product code, which is CAF for nebulizers, to understand if the device that is under development has previously been cleared or any version of it has been cleared or whether it can be used in an investigational study.

A drug specific inhalation device, for example, the antibacterial drugs that are relevant to the talk today, can be filed under a device module in a NDA or it could be by seeking a separate 510(k) pathway with the Center for Devices to clear it.

So as I have mentioned in a couple of slides back, orally inhaled drug product almost always involve multi-center review, because antibacterial the main mechanism of action is in the drug. CDER takes the lead and they send us a consult in CDRH to review the device component of the drug product. In case there are any biologics, CBER gets involved. And depending upon other constituents of the combination product, different parts of the FDA get involved in the review of the product.

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From a device review consideration for an inhalation device, when it is at our end in CDRH, we look at the indications for use for that device; the device description; the performance of the device when teamed up with the drug; the bio compatibility; if the device has any electrical components, it's safety and EMC; if the device has any software, the software validation data; human factors of course; and the labeling of the device within that combination product.

Indications for use is one of the most critical definition of what is actually that product; it's the intended use, what it intends to treat or mitigate; the patient population, is this drug and device labeled for adults, pediatrics, geriatrics, neonates, infants, because depending upon that it would define the performance required for that device when it is with the patient as well as the environment of use. If it's a home use device, a healthcare environment use device, can it be used in transport? Because that would impact again the testing required to support the safe use of the device.

From a performance testing perspective, we

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define an inhalation product to generate a respirable fraction. But how do we actually understand if the device and drug can interplay successfully to generate that respirable fraction that will be inhaled? We use a bench test -- well, we review the bench test that the sponsor submits using cascade impaction.

The figure on the right is an Andersen cascade impactor, which is basically a set of sieves that would partition the aerosol being generated by a device into these various stages that are defined by various cut offs. So anything less than 5 micron in size is believed to actually reach the patient's lungs and get absorbed and this test would help us understand that the device can successfully generate an aerosol plume that can reach the patient's lungs to get absorbed.

We do request that the testing is done at minimum, nominal and maximum flow rates that are allowable by the device to predict all use scenarios that the device can be used in once it's with the patients.

In case -- we also of course request that the sponsor addresses variability, sufficient sample size,

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appropriate confidence level. But if there are spacers being used or if there is a face mask being used, especially for children less than five years of age, our testing, our review consideration would also involve that, that the testing should be done in typical use scenario when the data is submitted.

Biocompatibility is the safety of the material of construction of that device that would interact with the patient's lungs. Because anything that's getting generated by these inhalers and nebulizers that are actually going to get into the patient's lungs, we consider them externally communicating with the patient's lungs. The type of contact, for example, if it's surface, if it's mucosal and for lungs it's externally communicating, defines the kind of testing the devices need to be provided with as well as the contact duration. If a nebulizer is indicated for 20 minutes use one time, it would have a different type of contact versus a nebulizer that is chronically indicated for 20 minutes every day as long as the patient needs it. So that defines the duration.

To know more about biocompatibility there's a

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guidance for industry that talks about the use of 10993, our standard for Biological Evaluation of Medical Devices.

If a device that is being considered for inhalation is already out there in the market, there is a process in which the sponsors provide us with just material certification for formulation on processing and the whole bench testing does not need to be done, because then we leverage the data that is already available for us to determine the safety of such devices from a biocompatibility perspective.

The particulate matters as well as the volatile organic compounds that are getting generated inside this device when they are being used also come into play when we are reviewing the safety of such devices. What kind of contact it has? Whether it's being used with a humidifier? Because the kind of contact would change when it's interplaying with the drug solution, the humidifier, et cetera. So all these considerations come into play for reviewing such type of devices.

If there are accessories involved, if, for

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example, a face mask is involved, biocompatibility should be supported for the face mask also. And finally, all testing that is included should be only on finished device that is to be introduced into the commercial market.

As I mentioned before, most of our nebulizers have electrical components, so we have a set of standards provided on this slide that determine the safety of these electrical components as well as the EMC.

In case there is a software involved in the device, there is a set of testing that needs to be submitted to the FDA. And this guidance for industry in front of us talks about how we determine the level of concern of the software that the device may have. For example, a level of concern for a nebulizer may be lower than the level of concern of a software in a ventilator device. So this talks about how to determine that and the kind of validation data that needs to be provided, the cyber security that needs to be provided to support the software in these devices.

And finally, we had a very good discussion

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about the human factors and I just want to mention that we've already talked about. But from a review perspective, we have seen that for inhalation products it's 10 percent medication and 90 percent patient interface to actually have a successful drug delivery to the lung when the device in the patient's hand.

So the case study that I have in front was without actually discussing the sponsor. A sponsor developed a new nebulizer technology that was for delivery intended for this one specific drug and they came to us at the Center for Devices asking us that they would like to file a 510(k) for this. And they actually came in really early before the development and we had pretty early collaborative talks. And we were actually able to share with them that if your device is being indicated for this specific drug, you're not intending to indicate it for general use, you may able to file everything and submit all the data that you have specifically in the NDA if you choose to and not actually have to submit a 510(k) for a device, because that's a drug specific device now.

And of course, this was an early communication

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example which was successful. And the methods that are available to actually do that for Center for Devices are through the pre-submission process. And for the Center for Drugs and Center for Biologics evaluation, we have Type A, Type B, Type C meetings that are available to interact with us early on.

There is also a guidance that is available from CDRH and CBER that talks about the request for feedback on medical device submissions to help the sponsors so we can collaborate early and help guide the development.

In conclusion, the inhalation drug delivery is dependent on a successful interplay between the drug, the device and of course the patient use. The review that we do at our end is grounded by the regulations -- we have our Code of Federal Regulations -- it's grounded by the standards -- in fact at Center for Devices most of our review work is development of standards and that defines how we review the devices -- and of course risk analysis of these devices when they are being used with the drugs. We strive to work with the sponsors to ensure safe and effective devices are

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available to the public. Thank you.

DR. NAMBIAR: Thanks, Deepika. Are there any questions for Deepika? Jeff has a question.

DR. ALDER: I'd say probably the majority of people developing new inhalational therapies think they have a unique drug or a unique aspect and they seek to make use of an existing device, only to discover at some point that CDER has concerns about the device. So is there a process of a formal review of existing devices and how can we communicate that?

DR. LAKHANI: So if you would just like to seek feedback for the device, for the drug device combination, the CDRH re-submission process is available wherein you directly contact CDRH and you reference the IND or the NDA that you've filed in CDER, which you don't need to go to CDER because we'll only be discussing the device. And of course, our 510(k) database would share what kind of general use devices are available.

As far as the INDs that are using devices that are not yet publicly available, the information is hard for the sponsors to avail in a public domain. But if

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you have cross reference that this IND uses this device and the patient population, for example, is adults only as it has been used in a previous clinical trial and the environment of use is home or hospital only and the intended duration is similar, I think most of the time by only providing performance you can leverage all the data that has been used before for the previous approval. Is that helpful?

DR. ALDER: Yeah, I think the message is early communication --

DR. LAKHANI: Yes.

DR. ALDER: -- both within FDA divisions and with the sponsor, because in some cases it has been late in the game that either a human factor or a performance issue has been discovered for a device that was already approved. And sponsors assume if a device is approved it must be okay and then they discover later that it's not okay and then try to retrofit human factor or other studies in.

DR. LAKHANI: Yeah. And the primary reason for that is that the intended use at times is different. Although it is an inhalation product, we

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may have a change in the patient population; for example, it's a switch from adults to pediatrics. So the way we would look at the biocompatibility of a pediatric, a device intended for pediatric use would be slightly more safe testing versus when a device is intended for adult use with respect to biocompatibility. So it's just one example.

DR. ALDER: Well, for today it's actually the other way around. It wouldn't be devices developed for CF. So younger patients that are now being -- try to use for NCFB, where the patients tend to be older.

DR. LAKHANI: Absolutely.

DR. ALDER: Yeah.

DR. LAKHANI: Yes, absolutely. Yeah.

DR. NAMBIAR: And, Jeff, there's also an opportunity when a submission is sent to CDER to the Review Division that you can ask device-related questions. And there's an opportunity to get input from CDRH very early in the process as well. So we do consult our colleagues in CDRH and we've -- there's many instances where we've had device-related questions and discussions very early in development and that's

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something we would certainly encourage.

DR. LAKHANI: Yes, please?

DR. NAMBIAR: There's one more question for you.

DR. AKSAMIT: And did I --

DR. BARKER: You discuss therapeutics. What about diagnostics? Specifically, I'm thinking of pulmonary function equipment. I was discussing with a manufacturer a month or two ago. They're developing a new software program for pulmonary function and they said that it had to be reviewed by the FDA. Does that fall under your purview or is that somebody else?

DR. LAKHANI: If it's an in-vitro diagnostic, we have a separate office for IVDs, in-vitro diagnostics, that review it. And if it is something like it's a device with a software, as you're mentioning, for PFDs, it would again be a collaborative review. So we would be looking at the device specifically. Or if it's a software only for an IVD, in-vitro diagnostics group would be looking at it.

DR. AKSAMIT: And did I understand you say that there's a different safety threshold for

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pediatrics than there is adults?

DR. LAKHANI: Just from a review -- just from a device material perspective. And I can elaborate that a little bit. The kind of testing that we would need for a new material of construction of a device for an adult would be slightly different than that for pediatrics, because of the vulnerability of a pediatric population is different than the adult.

The testing can -- like, for example, if the sponsor is doing extractables and leachables testing to support the safe use of the device and the material of construction, the kind of risk assessment that you would do would be different because the margin of safety is different between the two sets of population.

So the guidance that I talked about talks -- actually divulges way more into it than I could actually get in for today's talk. Even from a performance standpoint, the way a pediatric patient inhales, the maneuver for that inhalation effort is different than how a adult patient would inhale. So when we are looking at performance testing even by simple cascade impaction, the flow rate that we would

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be testing for an adult would be different than that for a ped patient. So that's how we look at the devices.

DR. NAMBIAR: I think, Deepika, there's one more question for you.

DR. LAKHANI: Yes, please?

MR. ZIMMERMAN: Is there any patient input in the early discussions during the drug development?

DR. LAKHANI: Not during early discussions. Mostly when the sponsor comes in they have information that they have discussed with the patient, they may have an early study that they want to present and just share data, but the patients are not involved at that stage.

DR. NAMBIAR: I think there's one more question for you.

MR. HAWKINS: Thank you. Is there a place for patients to come and -- after the drug is already approved? I have one drug that I take that I find very difficult to use the device. How do we deal with that?

DR. LAKHANI: Most of the devices or products that are cleared they carry a helpline number and we

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have -- like it's up to the patient to actually contact the manufacturer. And it is our understanding that the manufacturer strives that the device is successfully used by the patient. But over here also we have the whole role of human factors that's coming in that actually evaluate the use scenarios when they're evaluating the data.

And maybe when we're having the panel discussion, we could bring up again what you're asking and we could have Quynh involved with that answer.

DR. NGUYEN: Yes. So I just like to add that from a patient's use perspective, when applying human factors engineering process, the patient's involvement as the representative users of your intended product will be starting at the beginning of the process. So any feedback or discussions with respect to your use experience can be captured there very early on the design process.

In the event where you have issues with a product that's already on the market, like Deepika said, you can contact the manufacturer and file a complaint and that will go to the complaint database.

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And they would need to assess the complaints that they receive and whether or not that rises to a level that they need to report it to the FDA.

DR. NAMBIAR: Okay, great. Thank you, Quynh, and thank you, Deepika.

DR. LAKHANI: Thank you for your time.

SESSION 1: CYSTIC FIBROSIS: CURRENT LANDSCAPE, CHALLENGES AND CASE STUDIES

DR. NAMBIAR: So we move into our first session, where we will focus on cystic fibrosis and developing inhale therapies for cystic fibrosis. To start us off is Dr. Mishra, who is a medical officer in the Division of Anti-Infective Products and his busy portfolio includes a fair number of products being developed for cystic fibrosis. So welcome, Shrimant.

INHALED ANTIMICROBIAL THERAPY FOR CYSTIC FIBROSIS: A REGULATORY EVOLUTION

DR. MISHRA: Hello. Hi. My name is Shrimant Mishra. As Sumathi mentioned, I'm a medical officer in the Division of Anti-Infective Products. I've worked on a lot of -- or reviewed -- sorry. I've reviewed a lot of inhaled products that have come through our

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division and including several that have been indicated for cystic fibrosis indications.

So I want to talk very, very briefly just about inhaled antimicrobial therapy for CF and particularly just sort of point out some of the changes that are happening in clinical practice that are sort of making us as a regulatory division adapt to those changes.

So as I'm sure everybody knows here, the approved inhaled antimicrobial products for CF is pretty small. Obviously, TOBI was approved in 1997, and since that time, there has been several nebulized tobramycin products that have been approved, including Bethkis. There was a Podhaler -- TOBI Podhaler that was approved in 2013, which is basically just a dry powder inhaler version of tobramycin. And then in 2010, we had an inhaled aztreonam, Cayston, and that was improved. And both of these -- or I guess this whole, you know, class of drugs essentially are meant to manage patients who have CF, who have chronic pseudomonas infections.

Now, since that time we're seeing a little bit

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of an evolution in drug development; it's probably mirroring to a certain degree what's happening in current clinical practice. We're seeing different pathogens that are being targeted. We're seeing different drug regimens and combinations that are being used. We're seeing changes in endpoints that are being used in trials. And obviously all of that leads to substantial trial design considerations for us.

When you look at the question of pathogens, you know, obviously all of the initial development focused essential on chronic pseudomonas infections, CF patients. Now of course we're seeing other CF-associated pathogens that are being targeted, staph aureus, whether it's MRSA, whether it's nontuberculous mycobacteria or Burkholderia species. And these, you know, are a little bit of a challenge for the agency because in some cases the natural history of these pathogens is not very well known and also its potential impact is also not very well understood.

So it gives us both opportunities as well as challenges. Opportunities in the sense that in some of these cases there's a little more flexibility in how

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you can design your trial. So in some cases, you may be able to do placebo control trials. But there's also some challenges. So if you're going to do, you know, a comparator-based trail, how do you pick a comparator where there is no sort of known standard of care?

Now, when you look at drug regimens, again historically when there's development happening for chronic pseudomonas infections, at that time we're pretty much looking at singular inhaled drugs or antimicrobial drugs that were targeting pseudomonas in 28-day on and off cycles. And now we're obviously seeing much more diverse inhaled antimicrobial treatment patterns being used in clinical practice.

You know, a patient may be on several antimicrobial therapies, simultaneously targeting a variety of pathogens for a variety of purposes. Just looking at chronic infection with pseudomonas alone, patients may be on continuous therapy, where they're cycling from one inhaled antimicrobial therapy to another from month to month. And obviously that means there's challenges from a patient standpoint because they're using quite a few different devices from

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different manufacturers.

And just to give you an idea of, you know, again some of the things that are happening in clinical practice that we adapt to, you know, it's pretty much become standard of care to treat the initial acquisition of pseudomonas in patients with cystic fibrosis. Usually, this acquired in childhood and it's associated with long-term deterioration and pulmonary disease and survival. And basically, they've developed a standard of care at this point where they're using tobramycin inhaled 300 milligrams for a month and they follow the patient through serial sputum cultures or oropharyngeal cultures to monitor for both the eradication as well as recurrence.

And again, these are the types of things that are happening in clinical practice that we have to adapt to when it comes to trial design.

When it comes to endpoints, of course, you know, when you look at the TOBI trails, those were all based on relative change in FEV1 percent predicted. That was the basis for TOBI approval as well as all the similar drugs, you know, in that class. Historically,

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it was compared to placebo over 1 to 3 on and off cycles. And they were supported by important clinical endpoints, whether it was hospitalization frequency or time to antimicrobial use.

However, now you are seeing more consideration when it comes to trials given to other primary endpoints, whether these are from patient reported outcome tools and you saw some evidence of that in the Cayston trials or whether it's the use of clinical event such as service of primary endpoint where there is exacerbations and we'll again probably talk in more detail about the challenges with the exacerbation definition and whether to talk about frequency of exacerbations or time to exacerbations or whether using endpoints that's based on antimicrobial use. So again, quite different from what was originally used for the earlier trials.

So all of this basically gives us several basic trial design considerations. When can we ask for placebo controlled trials and for how long? How do we ensure the selection of a proper patient population? How do we separate the effects of being on multiple

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therapies and just the most basic question, which endpoints best serves a particular trial and how long should a particular trial be? So again, we sort of look at all of these changes as both good and bad, it's just we have to adapt to it and I think again Dr. Nichols is going to talk in much more detail about these changes that are happening in clinical practice. Thank you.

DR. FLUME: So thank you and I think we'll save questions to have for our discussion period unless there is something for clarification.

MR. FOLLMANN: This might be clarification. So it seems like FEV1 is sort of falling out of favor, is that because it's viewed as a biomarker, not a measure of what a patient cares about or why is it not so in vogue now?

DR. MISHRA: Right, so that's obviously an area of considerable debate. I think you are right. I think it has been viewed more recently as a biomarker and there is sort of difficulty in interpretation of what change in FEV1 percent predicted is actually clinically relevant. So I think we have seen a shift a

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little bit away from that. Of course, it's tricky because of course we know physicians whether it's pulmonary physicians, infectious disease physicians, they actually are using FEV1 percent predicted to make clinical decision. So it's a little bit of a tricky area for us, but I think we have tried to move a little bit more to more harder, I guess, clinical endpoints than just sticking with FEV1.

DR. FLUME: Thank you. I think there will probably be a lot more discussion about FEV1 when we get there. So I'm going to invite Dave Nichols. Dave, you've introduced yourself, is a pediatric and adult clinician taking care of patients with CF and he is the Medical Director of the CF TDN Coordinating Center in Seattle leading several trials and he is going to talk about current state and future considerations.

INHALED ANTIBIOTICS IN CYSTIC FIBROSIS: CURRENT STATE AND FUTURE CONSIDERATIONS

DR. NICHOLS: Thanks, Patrick. Thanks to those for the invite to present these thoughts today. As my disclosures listed there as asked, the most important disclosure is that a fair bit of this will be

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opinion, but I have endeavored to collect the opinion of several and what I present today is the majority if not consensus opinion in that regard and I'm sure it will be a nice start for that of others. I want to cover three main topics in the 25 minutes here. First of all, an overview as asked and what's happening now in the current state of CF care and then a view of what are the greatest focus of unmet need may be in developing new therapies in CF and then in that context what may be feasible and also viewed as informative to the CF community focused on key issues of study design.

So first topic, what's happening now. As was mentioned a moment ago, there are really two FDA approved inhaled options in CF, Tobramycin now available in several forms and then Aztreonam called by the name of Cayston. These were developed nearly 20 and 10 years ago respectively and they both target the same pathogens, pseudomonas aeruginosa which is clearly an important pathogen, but obviously not the only one that we are concerned with at this point. Despite this long term exposure, there is consensus opinion of ongoing clinical benefit with these drugs and that

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leads to pretty high prescription rates in our population. So here are our data from the CF registry, this includes about 30000 patients, about half of those on inhaled antibiotic therapy. On the x-axis there you can see time from 1996 to the most recent data available completed in 2016. What you can see is that Tobramycin had rapid uptake since it was developed in the late '90s and it has been used stably at about 75 percent of our patients for whom it is indicated. Then Aztreonam came on about a decade later, again had very rapid uptake and then has leveled off at about 45 percent of patients for whom it's indicated. So I suggested that we believe there is ongoing benefit despite couple of decades of exposure based in part on data like this, the study looking retrospectively at the registry. Again, across the x-axis you have years of follow-up and then they asked, was there any effect on mortality, perhaps our cleanest outcome measure and long term analysis, the survival is on the y-axis there and what we see after trying to control for baseline differences in these groups, there is about a 35 percent reduction in mortality in the users of inhaled

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Tobramycin versus non-users.

Shifting then to how patients are using these inhaled antibiotics, which was alluded to a moment ago. Going back on 2009, you can see that the aminoglycosides which is almost entirely Tobramycin in our case significantly dominated use, Aztreonam was just coming on board, shown there in yellow and then Colistin which is more of a grandfather product, it's actually very commonly used abroad, less so in our country, but a fair number of patients do use Colistin. What I'm going to show you is over time we are seeing some shifts here. Tobramycin continues to be very favorable and commonly used Aztreonam shown there in yellow is increasing, but the overlap is important to see. So there in the green and some of the other small sections, you can see increasing use of more than one agent by our patients. So the key point here is that Tobramycin now available in multiple forms and generic which is fairly recently made available and there is some push by payers to use that version, is the most common choice. We are seeing increasing use of Aztreonam over the last decade. Colistin in remaining

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mainly an add-on therapy and a lot more use of more than one class of inhaled antibiotic by our patients.

At this point I want to point out for those who may not be aware, inhaled antibiotics are used for two primary purposes in CF and the first is actually quite successful at eradicating early pseudomonas. It's commonly done with one drug for one or possibly two cycles. As was pointed out, a cycle is often four weeks and that's about 85 percent effective at eradicating the pseudomonas from the culture at least. The second and the more commonly appreciated one would be chronic suppressive therapy where this is now one or often more drugs that are cycled. So if we ask, what characterizes this group of users who are choosing to use more than one class of inhaled antibiotics? So they are not cycling so much on and off as on and on and on and on, staying on those drugs. There are often some adult, although that includes our adolescent population, they have modestly lower lung functions, FEV1 percent predicted of 70 percent or less. They have consistently positive pseudomonas cultures, so we are more confident that they are chronically infected

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and not intermittently infected as we can see sometimes and they may be experiencing pulmonary exacerbations even as little as one or more per year.

The point I really want to hit home here with this though is this group actually describes a fairly typical or desirable study population for inhaled antibiotics given what we have used in the past. So if we were to take this 2016 registry data and apply this very high level entry criteria, age greater than 12 or more, FEV1 of 25 to 75 percent of predicted which has been commonly used in studies, the DryPowder went up to 80 percent of predicted and then one or more acute exacerbations in the last 12 months. You see that there is even more overlap, more than one use of an inhaled antibiotic product is now the majority selection in this patient population. If we take that and then ask how many have demonstrated an ability and an interest to do clinical research, how many have participated in a randomized control clinical trial since 2010, the numbers get concerningly small at times, there is even more overlap there.

So let's take an experience just briefly, a

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hypothetical new drug study using these historical key eligibility criteria to try to define new study population. We would predict that four out of five would come into that study using inhaled TOB clinically and three out of five using inhaled Aztreonam and most of those would be cycling between two drugs, often these two drugs to avoid an off period. And then if we restrict that to those who have interest and ability to do randomized control trials, we get down to about 800 who are using CAT or continuous cycle therapy, another 500 who may be cycling on and off of a single agent.

All right. So we will revisit that in a moment, but let's shift then to where we view the greatest focus of unmet need may be in the current area, in CF. First question might be eradication. I have suggested to you a moment ago that this may not be the greatest focus of unmet need because our current approaches are actually quite successful and we have care guidelines now and really two effective treatment options that lead to eradication in 85 to 90 percent of the cases. There are data really just emerging now to suggest that at least with IV antibiotic therapy, you

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can help to rescue some of these who feel they will eradicate with inhaled antibiotic therapy alone. It's less clear to us in CF if the addition of oral antibiotics adds significantly to that of inhaled therapy alone. How about those who initially develop persistent pseudomonas aeruginosa infection, but are otherwise clinically doing okay. I would argue that this is not the greatest focus of need because again we have two safe and effective antibiotic options. We actually have a number of delivery device options including DryPowder, high efficiency nebulizer devices et cetera. It's a point to note that additional agents in this space I think could be appreciated and used actually, but if we are asking what is the greatest focus of unmet need, I would argue that this is not it. However, those who have chronic pseudomonas and are experiencing ongoing clinical decline, I would say yes, this is our greatest focus of unmet need when we consider how to develop additional therapies in CF because as I have suggested a moment ago, they have long term exposure to really all of their approved agents and they are showing clinical decline suggesting

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that what they are receiving now is not entirely effective and so we would clearly like the opportunity to test new approaches to treat these patients.

Lastly how about other CF pathogens who may be experiencing clinical decline and again, yes, I think this is an area where we have unmet need. It is more complicated and as was suggested a moment ago, there is less certainty about some of the pathogenicity and even more so the effect of treatment in this space, but clearly an area of further study. Also, worth noting that many of these patients are co-infected with pseudomonas and so may be receiving treatment for their pseudomonas pathogen. It's a little bit difficult to get hard numbers on this, but I estimate based on what I see that about 50 percent of our MRSA patients also have pseudomonas.

So this is a snapshot taken down from the CF Foundation registry, it's a portion of what we call a drug development pipeline. The point I'm showing you this today is to demonstrate that we in the CF community have been able to partner with sponsors to complete phase three clinical trial testing for a

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number of agents in recent years, some of them leading to full FDA approval and more so the group there on the bottom, a number of other drugs moving through who have reached human testing where we in the community and the sponsors are continuing to demonstrate an appetite for new therapies that we developed in this space. It's notable to me that a number of these additional agents being developed are actually pathogen agnostic and that may simplify some of the concerns about some of the special pathogens that have prevalence rates that are quite a bit lower.

To digress just for a moment, there has been a lot of attention about the special pathogen. It's worth noting we have seen increased prevalence of these, we are paying close attention and some of us have a particular focus on these MRSA, for example, more than tripled in prevalence between 2001 and the decade to follow, grateful to see that it seems to have stabilized in the last five years. NTM is one that has gained particular attention, we are seeing quite a bit of interest and in fact attempts at drug development in that space and the rate seem to be going up. These

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data probably underestimate the overall prevalence because they are based on culture and sometimes our patients are unable to provide good samples for culture. There are a number of others listed there and so that's pointed out here, again taken from the registry 2016 data. You can see over time on the x-axis and then the percentage of individuals on the y-axis. So we have drugs, FDA approved drugs for two I would argue, pseudomonas and even MDR pseudomonas, but none of these others that we tend to track and so that's a clear and obvious area of continued investigation.

So this limited availability of options plus this perceived clinical need has been accompanied by quite a bit of off label drug use. This is a snapshot taken down from a very popular central pharmacy used in CF around our country and I just want to point out that this is described as safe for patients and is compounding, not available commercially and then they list 11 different antibiotics, commonly compounded for providers and our patients.

To summarize this area of unmet need, again

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the limited approved options with nothing really developed to approval for about 10 years is notable, but this does seem to be largely meeting the needs for eradication and even our early pseudomonas patients who are otherwise doing okay and the real focus of need at least in my view and those I speak with is those with chronic pseudomonas and clinical decline because they are using the available therapies that they have and continuing to struggle with their health. Off-label use in that full development pipeline, I think underscores the desire and effect and ability for more safe and effective options and then special pathogens do deserve attention and they will have some unique challenges and uncertainties that we will need to address.

So then let's take that and shift to what may be feasible and informative to the CF community. Clearly this is an area of opinion. Hopefully it will lead to further discussion today. The question has come up about placebo controlled trials and again 28 days would be our typical intervention period or phase. It's notable here that those who get placebo are going

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to be off of any active drug for longer than 28 days and so we need to pay close attention to that run-in period and very aggressively sure design might allow two weeks which would ask for 42 days without an active drug and more traditional design will be four weeks, which will be at least 56 days without active drug. That period after is also important. If you require no drug therapy during the safety follow-up phase, you are asking for a further or increased period of time without active drug and those who get randomized to placebo and therefore it's going to be even more difficult to recruit patients to become interested in such trials.

I have shown already that most patients will be eligible and likely interested in these studies are going to be on continuous cycle therapy. So they don't have any breaks in their inhaled antibiotic period during routine clinical use and that smaller population who may be cycling on and off typically only go 28 days without their inhaled antibiotics during regular clinical use. So we have to focus on that run-in period and the follow-up. Stretching this to a design

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that is more reflective of what we saw with TOBI where we had, say, three cycles on and off and placebo controlled studies is likely to be not feasible in US or US like population. But I want to emphasize that despite these challenges, we in the community view the shorter placebo controlled trials focused on efficacy as important to do and also feasible.

Second point I'd like to make regarding study design is that blinding is going to be problematic for active comparator studies. So if we were to consider a blinded active comparator study, we would really be talking about a double dummy current versus new drug and that's not even bringing in the complication of continuous cycle therapy and doubling up on inhaled antibiotic during the cycle. So one would have to initially recruit a population on a unified drug and dosing regimen which is not going to be entirely straightforward given the increase in options. It's important to note here, the blinding may fail, our group is very familiar with their inhaled products and when you are nebulizing a product, there are much more consideration about blinding, you have taste and smell

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and appearance of a nebulizer, that's much more difficult than a tablet or an over-encapsulated product and this is going to present high complexity and burden not just for sponsors, but participants who are going to be dealing with multiple dosing regimens, two versus three times a day, multiple delivery devices and cleaning regimens, keeping track of your dosing times, that's going to challenge and increase the complexity and it's going to risk the poor quality data. So this needs to be considered if you want to think about blinding. In truth, in my view and in the view of those I talked to, it's probably not very viable or feasible design at least a very long study in our population.

Thirdly I want to point out that the effect sizes in some of our key outcome measures, may be diminishing and that doesn't necessarily suggest that the drugs are less potent than the drugs that we have currently available. So lung function, I'm glad to say is increasing in our population, these are data from 2016, so now nearly two years old, but shows you this is the adult median FEV1 has really approached 75

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percent of predicted in our adults and that is the upper end of the entry criteria for many of our historical trials. So if you stick with those criteria, you are going to have some difficulty in finding eligible patients, but more importantly the point I want to make here is that higher FEV1 has been associated with less movement or improvement in response to inhaled antibiotics in the trials we have seen. So this effect which is good to see may diminish some of that FEV1 signal and if we think about exacerbations, these are data showing age across the bottom and then incidents, so an annual incidents and asking did these patients have an exacerbation that required IV antibiotic therapy in the last 12 months. It's less than 50 percent on patients across all ages. So you are often left with this choice, do you want a large study predicting low incidence or do you want to try to limit your eligibility to enrich based on a history of exacerbations for example. I think it's worth pointing out here that this is a fairly strict definition of exacerbation requiring IV antibiotic therapy and there is a greater incidence if you

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consider oral or other definition such as physician decision to treat.

I also want to point out there we are now in a very exciting phase of CFTR modulator drugs really attacking the root problem in CF and we are glad to see significant improvements in baseline health. Based on what we have seen with the most effective drugs and what we have seen now in the phase two studies which are now an ongoing phase three studies, we reasonably predict that 90 percent of our patients will have drug indicated by their mutation that will lead to notable improvements in their baseline health. Bumps in FEV1 that are actually not just significant, but dramatic for us, 10 to 15 percent above baseline that's combined with significant decrease in their symptoms and the risk of exacerbation, further declining.

But these modulator drugs do not seem to be eliminating at least in our established pseudomonas population this challenge of ongoing chronic infection. These are data looking at our most effective treatment Ivacaftor in our most responsive population, those with G551D mutation and this is under clinical care. So

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there is a decline in the incidence of positive culture over time. They had a few patients who seem to no longer have positive cultures, but there is a big caveat in these data because many of our patients, in fact the large majority when they start these drugs go what we call dry, they can no longer expectorate and so the quality of our cultures diminishes and so we are not as certain that they have truly eradicated and a smaller study was done in a population with more consistent and clear evidence of chronic pseudomonas and they followed them more closely and over a longer period of time getting good sputum samples and you can see that they saw a similar pattern as we did in the goal study on the left where there was an initial decline in pseudomonas rates, but then there was a tendency to rebound over time and following them out just to about three years. It's a small group and this data are at times consistent, at times inconsistent and we are going to follow-up with some bigger studies to figure this out.

So in view of what is clearly a persistent need, but some challenges that we face, what data might

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be informative to the CF community and also feasible for us to obtain. I think we need to start with the assumption that a candidate drug is going to come in with strong non-clinical data that's going to indicate clear antimicrobial class effect. I think it will be ideal if that's done in some CF relevant models and that's an entirely different discussion.

I think it's important that the drug should have characteristics suggesting it's a good candidate for inhaled delivery. We have remarkably good track record of safety, two decades of inhaled antibiotics in CF and we don't want to risk that. We could add to that shorter placebo controlled trials as was mentioned focused on efficacy and really building on class effect. Despite some concerns about diminishing signal in FEV1, I actually believe that that will continue at least in the shorter placebo controlled and efficacy focused studies continue to be an important outcome measure. I think PROs are also potentially important and have a role, but that also deserve some further discussion today. And many of us believe that it's important to conduct these kind of studies in US or

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similar populations and then they could be partnered with longer duration open label active comparator studies, but this is mainly to focus more on safety and durability of effect. Safety signals I have shown there which would be obvious and durability looking at FEV1 over time and then you could pull in risk of exacerbation to some degree.

This begs the question, non-inferiority efficacy measures in some of these longer active comparator studies and that will be clearly helpful and could be assessed, but there are some important notable limitations that need to be recognized when considering this. First of all, as I've already mentioned it's going to be very difficult to do these in a blinded way and so you have to ask yourself at the beginning, are you okay with non-inferiority assessments and unblinded studies where you have long term exposure to the standard of care. I think fundamentally that needs to be addressed. Secondly, the effect sizes are going to be challenging to predict and may be fairly modest. Thirdly we lack data actually on our current common standard of care being the continuous cycle therapy to

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really define these in our margins, perhaps that could be overcome, but that's going to be a notable challenge in trying to develop these studies.

So that I'll just summarize. First of all, I want to emphasize that we do need and we in fact are working to develop new inhaled antimicrobial drugs in CF. I think sometimes there is a sense that CF has left (ph), you know, we've been doing inhaled antibiotic therapy for a while, that in fact is not the case. Improving health and practice patterns complicate feasibility of some of these designs, but despite that shorter placebo controlled studies focused on efficacy as well as longer unblinded comparative studies are feasible and we would find these useful in the CF community. Obviously, they'd have some shortcomings in regards to the rigor when we compare them to the original TOBI studies, but that's balanced by an ongoing unmet need in our patients and it's actually much better than what we have when making choices around off-label drug use which is pretty widespread and we'd prefer these to more traditional studies that would be done in parts of the world where

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CF care is far less aggressive and the patient population may be far less representative to our own.

So with that I want to thank you for the chance to speak today and those who really gave a lot of critical input to help design this presentation.

DR. FLUME: All right. Thank you, Dave. I think there is probably a lot of questions that you already laid out that we'll get to. So I think let's move right on to our next speaker. I'd like to invite Chip Hawkins up. So Chip lives with this every day, so that's a very important voice to hear, but he also has experience working with these regulatory meeting. So Chip.

PATIENT SPEAKER/PATIENT PERSPECTIVE

MR. HAWKINS: Thank you. So first I'd like to thank everyone involved with this meeting and most especially you scientists and doctors who are working here in this field. I'm 51 years old and as most of you are aware that's above the average for CF and I contribute a lot of that to the work that you guys are doing and committing your lives to. Thank you. As a CF patient, I thought I'll start by talking about the

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topic that I know well and that is the burden of treating CF on the patient. The awareness of the treatment burden on CF patients is a topic that's becoming more addressed in meetings such as this and also in talks and lessons I take to or attend or take part in at Johns Hopkins where I work. So in general, this is a good thing. I thought I'd share my experiences on the burden of treating CF from the patient's perspective.

I spend around two and a half to three hours per day on CF care, taking nebulizations or airway clearance or sterilizing the neb equipment. I also work full time which I understand isn't the norm for someone my age with CF, but I think more of us are going to be doing that and I try to do at least some of the exercise that my doctors are always bugging me to do. So, yes, my daily CF routine is burdensome. Yes, it is good that we are talking about this burden on treatment care. However, I just want to make sure that we all understand that it's much more burdensome to be hospitalized or to need home IVs or just to get sick or to deal with lung function decline. So no matter how

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much of a burden we think treatment may be or adding another treatment may be, it's always going to be better to add that treatment than to not based on a perceived burden effect.

So burden should never be a reason not to develop a new therapy or to not approve a new therapy. We can, however, talk about the formulation of what's being added as far as burdens go. When I said that I devote two and a half to three hours to CF care, what I should have said was I spend two and a half or three hours to CF care. I'm using TOBI DryPowder inhaler and Cayston which are the two drugs available to me, the TOBI powder takes may be a minute or two twice a day. Those months are the two and a half hour months. Cayston takes three to four minutes per dose three times a day and that's pretty good compared to other CF nebulized drugs, but still it's about 15 minutes a day plus those nebs need to be sterilized. So it really is that like a (inaudible) average two and a half or three hours per day.

I recognize that biochemistry or science probably has a lot to do or most of what's involved

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with choosing what form a new drug takes. However, as we are considering new drugs, we have to consider, is it the only factor, your cost involved or ease of producing the drug involved in these discussions.

Any drug that requires three doses per day is a burden and any drug that requires nebulizing three drugs a day is a huge burden especially for those of us who work full time or go to school full time and more and more this is going to be the CF population. Before the TOBI Podhaler was developed, I used to spend 40 to 50 minutes per day inhaling TOBI solution. I still remember even though it has been many years ago now when I first started taking the TOBI powder, that first day how fast it was and still being impressed at I have all this extra time available especially after work when I'm trying to getting on with my life after working a full day. Going to the dry powder form had a real impact on my life. For those of you who don't spent two and a half or three hours per day doing CF care or doing some other medical care, half hour may not seem like much. This is 14 hours per month on these Cayston months and quite a bit more hours per

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year.

Another way to think about this especially for the -- from the commercial point of view is right now there are no choices for me. There are two drugs that meet my needs and I alternate between the two. However, to go to all this meeting and hopefully future development is to make additional choices and really all else being equal, as a patient I'm going to choose the choices that are less burdensome and for the most cases that's going to mean dry powder formulations over nebulized formulation and twice a day formulations over three times or more times per day formulations. So it's not trivial, it's the way the patients, the future consumers are going to think about how to add new drugs to their regime.

Left phrase (ph), all else being equal, brings up another related issue to today's talk or today's meeting. I communicate with a lot of CF patients, same with the physicians during my various roles and I know there are a lot of patients who chose to skip doses of drugs or to even neglect their CF care. I've never had this problem. I like being healthy too much to risk it

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and I spend those two and a half to three hours reliably every day taking care of myself. I like feeling healthy too much. So far though this is made easier because there are no real choices. I take Pulmozyme because it's the only drug that does this role in what's available to me. Hypertonic saline may do something similar, but it's different enough that I take it as well and feel the benefit. I take the two available inhaled antibiotics and alternate between the two, so there is no choice there. However, the goal of today's meeting and future work is to make choices. This is a very desirable goal, but as a patient I'm going to want to know which choices are the best, not just that a drug works or appears to work and especially given how difficult it can be to even decide if the drug is working. What as a patient I'll want to know is if this drug is better than this drug, this is what's important to me. I get that it may not be possible to determine this during the drug development phases either due to the cost or logistics or even have enough patients to design studies that can address this.

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However, in that case I feel strongly that we need to develop ways to monitor this over time. I not being a scientist don't know how to do this or who should be doing it, whether it's the FDA or the Cystic Fibrosis Foundation or some other group, but it's important. Over time as more inhaled antibiotics come online and as an aside is more of the small molecule (inaudible) come online, we are going to have choices and without a formed scientifically informed way of letting patients know which to choose, we are going to end up choosing based on which is easiest to do or take or which is the cheapest or even worse which ones our insurance company says you have to take or even worse which ones have -- you know, companies that give out the best swag along with the drugs. And this is not the best thing for the patients. We really need to find a way as we develop new drugs to help patients and their physicians choose the best drugs for them.

Finally, another thought on that logistics and feasibility question and this is something that I think about, I don't know how much other people with CF think about this, this is my thoughts. I have taken part in

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15 or 20 drug trials, enough that I've kind of forgotten some of them and I started doing them because I'm really curious, I find them interesting. I'm in science or in medicine, I work Johns Hopkins, so I do this because I think it's fun, but I realize that's not probably the norm and I'm a little bit weird this way. I also want to develop better or help develop better treatments. I want better treatments available to me and I suspect this is why most people with CF get involved with drug trials. However, not enough people with CF taking part in drug trials, drugs trials are burdensome, they are uncomfortable, they are painful even, but they are necessary. So I spent a lot of time thinking about why more CF patients don't get involved and I understand they are painful and they are burdensome and we are already doing two and a half or three hours of CF care. So one thought I had, this is my thought, is with every drug trial I've been in, there has been some kind of payment, it's always a small payment, it's not enough to have an effect on anyone's life as far as quitting your job and being a full time drug study patient. But it's there and it

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makes me wonder what it is there for, what's the goal of the payment. If it's a recruiting tool, it seem too small. If there isn't something that we're going to address today, may be this is something that we should address right now, this is something that we should start thinking about. We need the patients to take part in drug trials. How many drug trials are being held up because there aren't enough patients to take part. I know several just at Hopkins that I've been involved with that were held for me for months because I had other health issues and there weren't other patients available who are willing to take part in those drug trials. So how do we deal with this? One way is to actually pay patients for their time in a meaningful way. I don't know how it's decided, how much should be paid to patients for their part in drug trials. I don't know if there are ethical issues, it seems silly though to say it's okay to pay a little bit, but not too much. It also seem silly to me to say, you are the patient, this is for you, so you shouldn't get paid to take part when we all found out with vertex how much money is there to be made with a

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new drug being developed and to say if patient is a part of that process. So maybe it's time to start thinking about better ways or different ways to recruit CF patients and to consider them a necessary part of the process and a professional part of the process. Again, that's a thought, I don't do this for the money, I know that's what we all say, but I don't. The amount of money I make on a drug trial is much less than I'd make working those hours, but a lot of people with CF work full time. So this is something to start thinking about, we need more patients. Thank you.

DR. FLUME: All right. Thank you, Chip. I think we are going to go ahead and take our break early, but I'm going to limit it to 15 minutes because we can have that time for our discussion because I'm fairly certain it will pretty robust. So I've got 10:03, so 10:18. And for those who haven't ordered their lunch, now is your chance.

BREAK

CYSTIC FIBROSIS TRIAL DESIGNS OF THE FUTURE: CASE STUDIES FOR CF INFECTION

DR. NAMBIAR: So we're moving to the next

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section of session one where we have two case studies. The first one would be presented by Dr. Allende. We'd focus our discussion on management of CF patients who are chronically infected with pseudomonas aeruginosa. So we've a brief presentation by Dr. Allende and then this time offer a panel discussion. That will be followed by a brief presentation by Dr. Mishra who'll focus on developing products for the treatment of chronic MRSA infection in patients with cystic fibrosis. So with that, so, Dr. Allende is a medical office in the division of anti-infective products and has been very involved in the development of several of these inhaled therapies primarily with non-CF bronchiectasis, but has also been involved with drugs being developed for cystic fibrosis patients. So, Maria.

PREVENTION OF EXACERBATIONS/ MANAGEMENT OF CF PATIENTS CHRONICALLY INFECTED WITH PSEUDOMONAS AERUGINOSA

DR. ALLENDE: Good morning. Thank you, Sumathi, for that presentation. My case is prevention of exacerbations or management of cystic fibrosis

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patients chronically infected with pseudomonas aeruginosa which as you heard from the previous talk from Dr. Nichols, it might be the focus of unmet medical need. So here is a hypothetical proposed development plan, sponsor A is proposing to use a novel inhaled antipseudomonal drug X to prevent exacerbations or to manage patients with cystic fibrosis who are chronically infected with pseudomonas aeruginosa and the population would include pediatric, adolescents and adult patients and the study design would be inhaled study drug X versus the standard of care which is inhalation and antibacterial therapy, for example, Tobramycin or Aztreonam and as you heard from Dr. Mishra's talk and Dr. Nichols also, these are the only two drugs that we have approved in the management of cystic fibrosis patients and they were approved in 20 and 10 years ago.

So here are the key protocol considerations, potential efficacy endpoints, changes in percent of percent predicted FEV from baseline as you heard from previous talks from Dr. Nichols as well. Changes in patient reported outcomes, CFRSD-CRISS or CFQR

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questionnaires, scores from baseline, changes from baseline, combination of the above or possibly other endpoints such as frequency, severity of exacerbation, prolongation of interval between exacerbations or time to exacerbation I'd say.

So the proposed efficacy evaluation would consist of a superiority or a non-inferiority hypothesis of study drug X versus the standard of care and the study population would select for high risk patients based on the age, treatment experience, baseline FEV1 and microbiology data. As Dr. Nichols emphasized, it is important to select a homogenous population with a unified regimen to allow for better interpretation of results. And another point to consider is the duration of the trial and the dosing schedule to assess the primary endpoint and compare to the standard of care, the current standard of care, multiple cycles or continuous daily use for six months or for more than a year.

So here I laid out some issues to consider, it's not an exhaustive list. No endpoints are validated with long term outcomes, although the percent

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predicted FEV1 is clinically meaningful, but it varies according to the timing and the amount of drops to consider, the rates of exacerbation vary by age and there is no established definition of exacerbation which also may vary by age group. Also, there is no data on effectiveness of the current standard of care, which is of a dynamic nature, continuously changing with new additional inhaled therapies.

So the non-inferiority versus superiority hypothesis have both the problem of difficulty in establishing a margin, an NI margin and this CFRSD, the CRISS scores are validated only in adults and children older than 12 years of age. I've to clarify that the two drugs that we have approved in cystic fibrosis, TOBI and Cayston are approved for adults and children older than six years of age.

And here are the panel questions, the first one, what is or are the clinically meaningful objectives for the trials. The lung function preservation, improvement of symptoms, decrease severity of exacerbations, decrease the number of exacerbations, a combination of these, possibly other

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benefits. What selection criteria would best target the study population most likely to demonstrate treatment benefit? What is the optimal primary endpoint and how long should patients be followed to assess persistence of efficacy or duration of efficacy and how should we monitor potential safety signals and risks, for example, resistance, the role of co-infections and emergent pathogens that will come up. So with this I leave up to the discussion. Thank you.

DR. NAMBIAR: Thanks, Maria. Sunita, maybe we can have the questions back up. It's the previous slide I think. So while we are getting the questions up, the way we thought we'd do it is we do have a full questions that we have outlined and this should essentially cover most of the important considerations where one is developing a drug for treatment of this patient population. So we can go through the questions, welcome questions, comments from members of the panel and also, we invite participation from members of the audience if you have questions or comments, please come up to the microphone. Dr. Flume, would you like to make any comments?

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DR. FLUME: Yes, I'd agree that we should take a pretty systematic approach to this and in my view, some of these questions are dependent upon how we address other questions, so to try to keep that in some sort of order. I think we heard very clearly from Dave and from Chip that there is clearly a need may be not for all the patients and I like how the patient here was presenting, that's probably the group that we are most interested in and we are in an evolving landscape, we learned this in the early phases of trying to do eradication trials, we learned it in the CAP (ph) trial and as we think about trial designs, feasibility will always have to factor into it. The perfect, say, design might not be able to enroll any patients, so we have to keep that in mind.

So in my view, a critical question for the CF issue is since we have approved products and you have seen the utilization is you are either going to be comparing to an active drug or you're going to be comparing to a placebo and so one of the key issues there is the blinding and so I'd just like open that up as an issue and see if anybody would like to share

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their thoughts on blinding.

MS. ELLENBERG: So this relates to blind -- it's not really a question on blinding, but it is a question, this is perhaps naïve because I'm not an expert in this area. But why nobody is talking about doing add-on studies which is what are commonly done in other disease areas where you have effective treatments, it's difficult to do a non-inferiority trial because you don't know what the margin is, but if you see that adding a new treatment to existing standard of care improves things, then you can conclude effectiveness. So you're doing a superiority trial, is that not a possible consideration in this disease?

DR. FLUME: So my first thought would be we get at a feasibility issue because in your example, you have a patient who is on TOBI and may be the question is, I'm going to do TOBI and drug A versus placebo and I think I heard loud and clear about the time that's spent and so add-on I think would be an issue of feasibility. I don't know if anyone else wants to add to that.

MS. ELLENBERG: I also heard that burden is a

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secondary consideration to improving health, so.

DR. AKSAMIT: In a related I want to ask my colleague, Dave, to expand on his slide about the utilization rates of inhaled Tobramycin since its inception and wide acceptance over this past 15 to 17 years there has been a flat usage even when the introduction of Aztreonam came along as an add-on, the utilization rates appear to have little impact. So there wasn't any waning or a decrease in Tobramycin use over that very extended period of durable utilization if you will for a long period of time, which may impact then how we approach additional (inaudible).

DR. NICHOLS: Yeah, I did want to comment. Thank you. I agree that the large majority of our patients would be unable to maintain a regimen where they have multiple inhaled antibiotics at the same time. Some of the complexity revolves around timing and how you do those, so trying to do two twice-a-day therapies or even a twice and a three times a day, it just becomes quickly unfeasible. There are some issues around the amount of inhaled liquid even being inhaled at a certain time, and so -- and I think for practical

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reasons, it's mainly the concern I agree that statistically it would be advantageous I think to be able to do that and I'm no statistical expert.

Quickly to the point, so this is my opinion, but I think that inhaled Tobramycin benefited being a drug where -- with which we had a long history of safety and effectiveness. It's a systemic antibiotic. We've used a lot and continued to use more commonly than any other when treating patients for exacerbation. There have been several products in more recent years that have been developed. They have probably helped to maintain 70 percent use rates, so the dry powder I think give it a boost. There have been generic products that have come to bear and smaller volume nebulized products.

So now multiple options. Some of the peer opinions or constraints come into place there too. So I think that's part of why -- I think it's important though to clearly state that I tried to show in the mortality data, again these are retrospective and one could ask questions around some of that, but the fact is despite this long-term use, we see ongoing benefit

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and clear outcomes such as mortality. And so there have been concerns raised for instance around the selecting for resistance and you can define that by MIC, so you can define that by a lack of clinical response. And we I think as a community have not seen that as an emerging problem today.

UNIDENTIFIED SPEAKER: I just want to thank --

DR. ZEITLIN: Excuse me, I would like to add a couple of things.

UNIDENTIFIED SPEAKER: Okay.

DR. ZEITLIN: One is that inhaled aminoglycosides over time have been associated with hearing loss in our CF patients, and so I think considering newer chemical structures that don't have those risks would be important and the add-on could be as a third cycle. I haven't heard anyone talk about that. Either it's tobras, aztreonam and then the drug A, or you put one of the others and take it out for the time that you study it so that the patient is always on an antibiotic would be two options.

DR. FLUME: So my question about blinding is if you are comparing to a placebo, and that's your sort

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of usual issues of blinding to make sure it's matched and I think Dave laid it out about short placebo-control trials, but if you're designing studies that have an active comparator, that's where my question is about blinding because I think I would agree with Dave going to double-dummy, double-blinded is a real buzz-kill for patients.

DR. DHAND: So, you know, we are only talking about drugs, but we heard about the burden of the disease for people who have -- take -- spend two and a half to three hours every day. So I think another option would be to look at newer devices and formulations which are more longer-acting. You know, we could have long-acting beta agonists now that goes for 24 hours. I don't see why we can't design antibiotic formulations that need to be taken once a day and what effect that has on the burden of the disease as well as the adherence to that I think would make a big difference.

MR. HAWKINS: Yeah, I think I agree with what you just said. You know, a dry powder formulation would not really add much to the burden if it can be

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done in that way. I can't express enough how big a difference that was between the two formulations. Also with the case in the three times a day, it's burdensome, but I think having to sterilize and nebulize it in a day is probably the biggest burden. So if we could be using disposable neb cups, that would reduce a lot of the burden if you can use a, you know, a 3-minute duration time for the nebulization part.

So I think it can be designed in such a way to add another antibiotic to your regimen without you greatly overwhelming us, if that's possible, you know, with the chemistry involved. Also thought I'd just mention as an aside in regards to blinding, I did a drug study last year in which I was off my -- one of my inhaled antibiotics for over a month, and I could feel the difference. So I don't think you could blind somebody just by giving them placebo because they're going to know that they're not -- it's that -- works that fast, at least with me not being on an antibiotic for a month after having used the double-regimen for years, I don't think you could hide that from the patient.

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DR. FLUME: I think that clearly speaks to some of the issues Dave brought up about the ethics or the stomach for doing longer placebo-control trials in those patients, but I'm talking about how do you compare a drug which is through an e-flow compared to TOBI which is through a Pari jet nebulizers. Dutch (phonetic)?

MR. VANDEVANTER: We're kind of dancing around the question you asked which was about blinding and I think we can just assume that your super-inhaler is drug A. The question is how do we test it and I think it's a mistake to think that sponsors are trying to get the lowest burden best delivery possible, of course they are. But the reality is, is that we cannot blind these treatments because the patients are familiar with them and so you could give a patient their Tobramycin as a placebo, but they would know immediately that it was a placebo. The blind would be effectively broken immediately.

In addition to the -- in addition to how the patient felt, it would be clear to them that it didn't taste right, it wasn't right. And so I mean we've come

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to the conclusion after going round and round on this that if we are -- and we do need extended safety data on these new drug A's, it's going to have to be obtained in an open-label fashion. It will ultimately be open-label whether we attempt to blind it or not.

DR. O'DONNEL: Patrick, go ahead. I was just going to say, you know, we're stuck in this month on/month off, or month on cycle, you know, continuous cycle. What about thinking about some other, you know, 2 weeks on, 2 weeks off, 3 drugs rather than just 2 drugs? I mean, we've landed in this world on both the CF and non-CF side of cycling without really much evidence, right, to begin with. So I just throw that out there as another option. I don't think you're going to get the answer in the blinding.

DR. FLUME: Yeah, so we know the history of how we landed at our precedent which we won't reiterate today. The -- and I guess what I'd like to do is maybe hear from the FDA because I heard from Dave that a short placebo-control trial might be tolerated and then a statement that, you know, there's going to have to be open-label comparator and how that would look in terms

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of both efficacy or safety.

MS. TRACY: Well, I'll just dive in here and say I think it's very important to understand what the objective is. Is it to preserve or improve? Is it maintenance or improving something? The patient commented that he felt a difference. I'm curious what you meant by that. Was that your lung function when you came off therapy?

MR. HAWKINS: I felt, you know, people will see us get -- maybe split up our lungs and they felt chunkier, I felt like it was more difficult to inhale full breaths. It wasn't dramatic like I was like dragging, I was doing my normal activity, but when it involves breathing you just -- you can feel a difference. And now I knew I was off the antibiotic, so I could -- in other words I could have been fooling myself, but I perceived a real difference. The pulmonary function tests were blinded, so I don't know if there was a real difference, but I just felt that perception of there being a difference.

MS. ELLENBERG: There are many areas, medical areas where we don't do blinded studies where it's not

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feasible where the drugs are -- have very distinctive side effects, I guess cancer, chemotherapy is the most obvious, one that we have managed to make a fair amount of progress. Nevertheless, I think the issue of blinding overlaps essentially with the issue of what the endpoint is because when you have endpoints that are very subjective, that's when, you know, not having a blinded study is most troublesome because the evaluation, whether -- especially if it's a patient-reported observation can certainly be affected by knowing whether or not you're on active treatment.

If it's a physician evaluation, one can think about having the physician who's doing the evaluation blinded, not knowing what treatment the person is assigned to, I don't know how feasible that is. That would suggest, you know, people wouldn't be evaluated by their own physicians who would have to know what's going on, but the idea that you can't do it unless it's blinded, I mean there are many areas where we study things that are un-blinded and we -- but we have to try and find an endpoint that's reasonably objective that we think is less likely to be affected by, you know,

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knowledge of what the treatment is.

DR. FLUME: So in there, because you can almost get into a chick and egg scenario because if we talked about endpoints and have that, then is blinding going to be tolerable and so forth, but the other aspect of that particularly when you have a drug like TOBI which has been in for years, you're enrolling patients to remain on TOBI, they already have demonstrated an ability to tolerate a therapy given that an advantage over whatever the comparator might be. So I guess what I'm taking from that is that for some endpoints, blinding would be deemed to be preferred, that might be an objective endpoint, like FEV1, but PROs (phonetic) or exacerbations might not.

MS. ELLENBERG: Well, yeah, I think for an objective endpoint, you could make a case that you could do it without blinding. And again that's -- I don't know how objective or subjective all of these things are, even things that are, you know, seem to be objective can be affected by, you know, somebody -- I myself have taken FEV tests, I think, you know, I might be affected on how I do on it depending on if I knew

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what treatment I was on. So it's hard to, you know, it's hard to completely rule out subjectivity, but some endpoints are clearly more objective than others.

MS. HAMBLETT: I think it's important to point out I think we have sort of two straw men on the table. We have maybe a more traditional duration study that would be 6 months, and we can only achieve that if it was active comparator versus a shorter placebo-control trial. The longer duration active comparator trial, if the active comparator that would likely be continuing alternating therapy. In that situation, we are likely talking a non-inferiority trial, I think it's safe to say either with an FEV endpoint or exacerbation endpoint, we're talking hundreds -- almost a thousand patients probably for that size of a trial versus a shorter placebo-control trial for superiority would be a few hundred patients at most. And so I think we should just keep that in perspective as we're evaluating those two straw men in terms of the need and trying to get, you know, the development forward.

DR. BARKER: Just a comment on the blinding, some of this -- how difficult this is, we're involved

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in the mucokinetic trial of Mannitol and there was huge discussion before the trial about what an appropriate blind -- placebo would be because Mannitol has a sweet taste. And after much discussion, the end was to give a very low dose of Mannitol as the blinding agent. So we did the trial, it was a negative trial, but the harshest criticism ended up being partly why was it a negative trial is maybe a placebo was actually partly effective. So you try to do the best you can and that's what you may end up with.

UNIDENTIFIED SPEAKER: Dean has a comment? Yeah.

MR. FOLLMANN: Yeah, I had a comment about blinding, but it's pretty much similar to what Susan made that basically in an unblended setting you want to have something that's objective and not so patient-driven. Another thing though I wanted to bring up, sort of related to Susan's comment about an add-on trial is have people thought about crossover trials for this setting, so for the trial Maria, you know, proposed, you'd have drug X or Y followed by standard of care. You could do that in principle for 6 months,

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then switch people who were originally on drug X to go to standard of care and vice versa.

Such trials can be more efficient than regular trials because each patient gets drug access as well as standard of care and they sort of serve as their own control and can sort of benefit from smaller numbers and be more efficient. So it seemed to me sort of a natural question to ask where this chronic disease where the therapy doesn't linger for years, it's sort of -- its benefit sort of stops when you stop it and you know, I was just wondering if people had thought about that or if that would be potentially feasible. It seems to me you could interrogate the databases you have and then sort of see how -- and then have a thoughtful analysis of whether it was efficient or not and work through the design because you have data to show what would be the advantage of people acting as their own control.

DR. TINO: Just in terms of the discussion about the add-on, I guess it's important to really define what you mean by add-on. The add-on to a baseline drug, do you add a drug during the same cycle

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of TOBI, or do you do add-on in the month off. And I guess what I want to bring up is what's the tolerability of those two combined drugs. And I'm not a CF doctor, but certainly the word on the street is that cystic fibrosis patients can tolerate inhalation therapy better than for example non-CF bronchiectasis patients, but are there concerns about tolerability with two inhaled drugs given at the same time, if add-on means add on to baseline therapy.

I wasn't specifically talking about add-on, I just, you know, because Susie was opening it up to more general design. This would be drug acts alone versus standard of care alone, and then switch over to the opposite after a period of time.

DR. AKSAMIT: And I would express some caution with using crossover design for bronchiectasis. Oftentimes if the event rate or whatever the endpoint is, is not a frequent enough event, it's really hard to capture that, and there is a temporal relationship with what's going on for the preceding 6 months going in, say, if it was a yearlong study, and so I think that would be problematic from a bronchiectasis standpoint.

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DR. FLUME: So I'm going to continue with the -- whether FEV1 satisfies as a objective enough measurement to meet. They also heard they had proposed a short placebo-controlled study and then a longer open-label comparator study. Presumably that shorter study would require endpoints that would be responsive in the short term and that's not going to be exacerbations.

MS. ELLENBERG: Would it be FEV1?

DR. FLUME: So could someone conceive of a new product that can do a short placebo-controlled trial with FEV1 as an endpoint for efficacy followed by David's suggestions of a longer open-label extension to give you some sense of durability and safety.

DR. NICHOLS: Yeah, I would argue I guess to answer your question, most inhaled antibiotics studies we've done and completed where they've been effective, we've seen the FEV1 bump between 7 and 14 days after starting and then a stability thereafter, sometimes a modest decline between 2 and 4 weeks. So that in my view is our most accessible short-term outcome measure. I think that the quality of life signal can change,

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it's just we're still working through validation of some of those two, so either of those to me would be the potential ideal outcomes in a low duration placebo-controlled study.

MS. ELLENBERG: Yeah, so that would also make Dean's thought of a crossover trial possibly feasible too if you would see an effect on FEV1 that quickly.

DR. NOONE: What about a microbiologic -- we haven't really talked about a microbiologic outcome. I know it's not a perfect outcome, but is it worth -- worthy of consideration in shortish to medium term?

DR. FLUME: Just based again, Dave had that pointed out good for eradication studies. That probably is the endpoint, but that wasn't really the unmet need that was defined for chronic infections, I don't typically think that the micro, unless you're looking -- you know, CFU reduction is typically a phase II clinical endpoint.

DR. NAMBIAR: Yeah, so we've certainly seen the use of microbiologic in the reduction of colony count as a suggestion that the drug works, but that really has not translated into clinical benefit

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necessarily. So it won't be adequate as an endpoint, but certainly it's part of the valuation of the drug overall. I did have a question. So Dr. Nichols, I think you brought up the point about, you know, a short placebo-control trial where one could do for short term. But in our discussions with some sponsors, you know, it has been mentioned to us that even that might be a challenge, and I just wanted to get a feel for what other panelists thought about the feasibility of even doing such a trial for pseudomonas specifically. I think staph aureus is a different discussion.

DR. NICHOLS: Just to see you've heard my opinion, I'll let others come, and I would -- I do believe that it's feasible if properly designed and not too large.

MR. VANDEVANTER: And we've done a lot of work trying to understand what our options are and I think it's the least bad option. And as Dave pointed out, really the 28 days off is not great. The problem lies if the sponsor wants to wash patients out for 4 weeks beforehand, and if they also want to have a 4-week follow-up period, now you're talking about 3 months off

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therapy, and it's just not acceptable. So I think where there's room for some innovation might be in actually taking patients as they're on inhaled antibiotics, enrolling them directly over to active versus placebo. And based upon what we've seen and actually what Chip said, for these patients that are on continuous therapy, if you take them off therapy for 28 days, there's some kind of signal there, and the question is how can you capture that signal in a randomized blinded population?

So I think our feeling is, is that these different endpoints are -- all comprise class effects for inhaled antibiotics, and the FEV1 change in and of itself isn't necessarily the gold standard that it has all of the benefits, but it's one of the class effects that's reproducible. And we assumed that if we can run a longer open-label study that we'll start to see these other effects, effects on exacerbation.

MS. HAMBLETT: Obviously those studies, a placebo-controlled study would need a built-in rescue end-point that would have to be incorporated. And I think, you know, why we haven't gone into crossover

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designs in the past is because we've been required to show efficacy with the exacerbation endpoint which requires a much longer duration follow-up. So if in FEV1 endpoint is sufficient, then, you know, we would be able to vet some of those designs and perhaps those will be attractive to patients because they would, you know, be guaranteed the drug. But also, a 20 days study, you know, rolled into an open-label, you know, a study would also make it attractive to the patients to have that new therapy available.

DR. NAMBIAR: So there was a comment and I think, Dr. Nichols, you had made the preference to get at least a reasonable number of patients that represent the U.S. population, so I just want to get back to the question of feasibility, so even in the United States, it's still feasible to do at least a one 28-day period, and whatever period we choose, that would be placebo-controlled.

DR. FLUME: I would think so, but I worry about the watch and where we're going to call it, so you heard Chip say that when he came off the drug, he began to develop symptoms, and from some studies when

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that, you know, period before they had randomized, there's a fair amount of screen fails often because of exacerbation. So patients were clearly developing symptoms. And so I don't know if it -- has been just a sponsor reluctance or if there was comment from the Agency about the notion of being on standard of care therapy until the moment of randomization. So technically if you put someone on placebo, they're now on a withdrawal.

MR. ALDER: Yeah, sure, you've thought about doing placebo studies, but here is one consideration. If you're putting patients on placebo and you know they have an active infection, the reason for doing that is you expect them to do worse than the comparator. That's the point of a placebo trial with a superiority design. So what -- however you define do worse, that has to be rescueable, and then there better be some benefit for the patients that are going to be in the placebo, and you know, some people, we, you know, try to minimize that by doing the 2-to-1 or 3-to-1 or whatever, so, sure, placebos are attractive from smaller patient numbers and more rapid meaning an

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endpoint, but there is still I believe a big feasibility in that medicine and CF has moved way beyond what we're doing in clinical development.

Majority of patients are on more than one drug, they're often on head to tail aztreonam and TOBI, or TOBI and Colistin or something, and now taking them off, there'd be altogether, right, this people have pointed out there's now a withdrawal and signs and symptoms, so that washout period has to be minimized, and the trial kept as short as possible. So I think there's ethical considerations as well as trial design considerations around a peer placebo. I think the add-on idea on the other hand is very interesting of doing head to tail TOBI plus something else versus TOBI placebo for example. Now you are not mitigating the standard of care, but expecting additional benefit. The downside to that is now it's a superiority design which has -- is we know pretty high hazard in the field of failing.

DR. NICHOLS: So we did that study. It was called the "Cap Trial" and it failed because we couldn't enroll, and the reason was is because patients

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were already doing a CAT (phonetic) regimen and their clinicians deemed it unethical to now put them in a randomized trial that might get placebo when they're already doing it as therapy. Now we cut the study short, we looked, there was a signal, but it didn't meet statistical significance. But I think what that showed is, is that the CAT regimen as a clinical trial design was doomed for failure.

MS. ELLENBERG: Taking a long view, and maybe -- again, maybe this isn't realistic, but would it be theoretically possible if you knew that another agent was -- if you were able to do an add-on study, I understand about all the burdens and all of that, but if you found that you could give to at the same time, is it conceivable that a combination product could be developed so that people would only, you know, be having one administration and not two? I mean, this has been done in a lot of areas. I just was in a conference on HIV where they compared, you know, somebody holding a entire handful of pills that people used to have to take and now it's one, you know, once a day.

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So, you know, if it would be -- if it's theoretically possible that combination regimens could be developed or people would inhale two, you know, at a time in the same administration, then, you know, then one might think harder about going through the tough part of actually showing that the second one works in an add-on study.

DR. FLUME: There is one example that was on Dave's slide of the pipeline. It's a combination of fosfomycin and tobramycin. The challenge you get in there is what are you targeting now because fosfomycin has activity against staph, for example, and then that gets into your patient selection and so forth. It becomes more challenging.

DR. NICHOLS: Yeah, I think that would be obviously attractive if it could be done. There are -- a lot of our inhaled products run up against osmolality restrictions, that's why they have to nebulize 5 or 4 mls instead of 2 or 3. So -- and then issues of compatibility with the two products. So I agree that that would be a terrific step forward, but again I worry about some of the logistics of pulling that off,

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not to mention sponsors having then potentially to collaborate in that way. I did want to comment back to the previous comment about ethical considerations of short placebo studies and clearly, I think we need to be mindful of that and in this way, I'm kind of cutting it both ways, but -- and explain how long-term exposure seems to still provide benefit, but we wouldn't be having this conversation if we didn't see perceived ongoing need in this population, right?

And so we have two approved agents, so we can do CAT in our patients. If all of our patients felt like that was working for them, then maybe this wouldn't be such of an unmet need until -- the point I'm trying to make is that despite the fact that these drugs continue to work for fair numbers of our patients, there are still large numbers of our patients who perceive that one or two of these drugs are not working well for them and so their willingness to participate in a placebo-controlled study with the potential benefit of getting a new agent in the study, but more so available that may work for them clinically I think is an important area to consider in the idea of

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an ethical conduct of a short placebo-controlled study.

DR. MISHRA: So my only comment would be in -- you know, if you were going to accept the short placebo-controlled trial with a longer sort of a open-label follow-on is that, you know, I think sometimes we worry from our -- the Agency perspective is that, you know, the open-label follow-on which is really for safety purposes is just sort of like a forgotten part of the trial, you know, where there's a lot of laws to follow up. And you know, we're lucky at least right now because we've used inhaled drugs where you know a lot of the safety issues beforehand and I think as you mentioned, you know, you have hearing loss in some of these patients who have been taking Tobramycin for a long period of time.

So you develop a product that's completely like a new molecular entity. You don't really know what the safety issue is, and really, you know, you're sort of telling these patients you're going to take these drugs for 20 -- you know, potentially 30 years, and all you have really is one sort of month that you did a comparative trial and maybe a little bit of

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safety information. So my -- you know, I think it's very important that the open-label portion of that trial not be forgotten and you've got some very good comparative data that, you know, as much as you can that you can keep people on the trial to get that comparative data is very important.

DR. BARKER: A comment back on FEV1, not a CF expert, but I think in the late 1990's with TOBI, the FEV1 delta was 10 to 14 percent. And 10 years later it was about half that, and I think more recently it's even less, the delta FEV1 in trials and our main argument for FEV1 has been sort of an old trend in reproducibility, but I'm wondering if we may be running out of sensitivity, that is our endpoint parameter.

DR. FLUME: Let's take that conversation to the endpoint, but just to give you some view on that, the -- that change -- that delta was driven primarily by adolescent patients, and if you look at the adult patients involved in that study, it was a small margin, I can't remember if it was 2 percent. And then if you look at the clinical trials over time, the mean age of participants has continued to increase, so it's gone

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from 18 years of age to 25 to 32, and so your focus on adult -- a population. And then in the study in which Aztreonam was compared to TOBI, a common slide shown was the flat response, the attained response to the Tobramycin, and an attempt, an argument was made that, see, it's lost its effect.

But you can't know that because you didn't take them away from drug. That would require withdrawal study and you might have seen them get worse actually. So it doesn't mean that the drug isn't working. But let's talk about FEV1 and a comment then.

MR. HAWKINS: I was just going to comment, when the burden that get real quickly, you have people taking -- involved in a drug trial expect to be burdened. So we did the add-on of even 20 or 30 minutes per dose, it isn't what I was referring to when I was discussing the burden. I was referring to what the eventual therapy is going to add to our lives. So I don't think we should worry too much if, you know, a doubling-up type effect. I -- strategy is what we choose that the patients who are going to take part in these studies are not going to be doing it by that, I

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don't think, so back to the FEV1, sorry.

MS. HAMBLETT: No, I mean I was just going to comment that FEV1 offers us a large opportunity to do a feasible placebo-controlled trial and that -- recognizing the ethical issues when we weigh that against the size of that trial, and then need to, you know, how many patients we would have to recruit, you know, that could be around 125 patients that that could be done. And if we're looking at a drug that would need to have a robust effective, say 5 percent or something.

And so I think that that, you know, makes that more feasible, you know, paired with obviously you need a lot more data on safety that -- so it's not sufficient just to roll over those patients into an open-label study, you would need to recruit additional patients for safety, for long-term safety. Paired with that, I think, you know, we also have a robust CF registry, patient registry that offers even longer follow-up and as well as data across the entire CF population that would eventually be on these therapies that offers us the opportunity to look at long-term

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outcomes, you know, independent of sponsors or provide data for post-marketing studies as well.

DR. NAMBIAR: So I would like to hear from the clinicians. I mean, I think it looks like the population that we really need new therapies for are treatment-experienced patients because those we do have some options. So in that group of patients, what kind of benefit are we likely to see even with a single -- you know, a one period where they can -- we can get some placebo in terms of FEV1 or other potential endpoints because I think the point that was made earlier, you know, is very true. In the earlier studies that were done the magnitude of treatment effect was much larger, but over the course of the years, you're seeing that magnitude is much smaller. So even if move towards an FEV1 endpoint, do we anticipate that there would be a reasonable treatment benefit in that highly treatment-experienced patient populations?

DR. FLUME: So that's -- always the question is when -- what's the magnitude of benefit that's clinically significant. And as a clinician of course

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every day that they don't drop is a good day. So anything greater than zero is better. But then you look for precedent and I'll just look to the recent CF tier modulator studies in which the magnitude of benefit was in the range of 2 to 3 percent. And that wasn't raised as an issue in the evaluation of that panel as whether that was clinically significant. So does that establish a new bar? I don't know. Obviously, you'd like to have other compelling endpoints that add on to it that shows there's another clinical benefit besides just a 2 or 3 percent change.

And that was in actual -- absolute FEV1, not with a relative whereas those earlier studies, that 10-plus percent that was relative change in FEV1, was it not? And Pulmozyme was approved with a 5 percent change in relative FEV1. So that would equate to roughly about a 2.5 percent absolute change. So although commissions may have as number 5 in their head, the actual number probably is in the 2 to 3 percent range.

DR. O'DONNEL: Can I ask project -- my CF colleagues here, I mean could you have a trial to

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enroll the failures on the current treatment, the -- whoever you deem to be CAT failures, or intolerant of the current regimen? Because that's who you're looking for, right, but are there enough of those patients and you could --

DR. FLUME: I'm going to toss that question to Dutch because he had done an analysis on exacerbations, and in a recent example of one of the products that is in that pipeline which was inhaled levofloxacin where exacerbations was used as the endpoint and didn't hit, but then looking at the history of exacerbations, and so I think it's kind of getting to question number 2 here which is trying to lean towards who you're trying to recruit for the study.

MR. VANDEVANTER: Yes. Hi Ann. So what we see in this population is even amongst patients that are receiving continuous inhaled antibiotics, there's a sub-population that continues to experience pulmonary exacerbations. And we -- and it's not clear that a more effective antibiotic therapy would reduce that, but that's certainly the population where both the patients and the clinicians are seeking alternatives.

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But defining of failures sort -- short of complete intolerance or allergy is actually pretty difficult in this population. They have a lot of morbidity. These are patients that have advanced lung disease. They've had -- they suffer exacerbations frequently, and so they don't present themselves as obvious failures, but if you look at their chart over the past couple of years, you can see that there's definitely room for improvement. The challenge there however is that we don't have a good feeling for how effective their current therapy is, so comparing this therapy to that, so in any kind of non-inferiority setting is really difficult.

MS. TRACY: That's superior.

MR. VANDEVANTER: Well, superiority be great.

MS. TRACY: Yeah, just to jump in there, I mean that sounds like a population that you want to see an improvement in symptoms, and so that would be a superiority design presumably?

MR. VANDEVANTER: True, but we would be looking for the superiority based upon longer term outcomes, exacerbations or something, so not in a FEV1

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setting necessarily.

DR. DHAND: So one population might be the people who use the triple antibiotics regimen and you know, instead of inhaled Colistin could be use drug X to see if that improves the exacerbation rates or functional decline.

DR. LIM: That is -- this is Rob Lim from DPARP. I just wanted to add a point of clarification, Dr. Flume's point regarding the CFTR modulator with a 2 percent -- 2 to 3 percent improvement in FEV1. I think, you know, it is true that that was a primary endpoint at one on that, but the advantage we had in those studies, if I assume you're talking about lumacaftor --

DR. FLUME: Yeah.

DR. LIM: -- is that those trials were long enough when we could look at other clearly clinically meaningful endpoints, it wasn't just a 2 or 3 percent improvement in FEV1, we saw improvements in other parameters, and in my mind one of the important ones was improvement in exacerbations, so it wasn't just that -- just that number alone, it was -- it had a lot

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of other supportive data which was really only attainable because the trial was long.

DR. FLUME: And I understand and I agree with that, and -- but if you're left with you can't do a 6-month placebo-control trial, can you have a short so you hit your -- look at your FEV1 endpoint and then you're looking at your other endpoints from open-label comparator, and that's where it gets tough because now you're looking at exacerbations or PROs, and you know, maybe you can look at FEV1, but there's a lot of things that flex into that. So is there any comment on these other endpoints?

DR. NICHOLS: Yeah, just lastly on FEV1, that's an important point. What I've taken away from that lumacaftor/ivacaftor study in part is that we know these modulator drugs can have significant impacts on FEV. We see with ivacaftor 10 to 15 percent and so with luma-iva we saw about a 3 percent absolute increase and yet that led to nearly 50 percent reduction in exacerbations, 30 to 50 percent and that is notable for us and so I don't know that one can easily extrapolate from the modulators to inhale an

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antibiotic therapy, but that's a notable kind of link there that I find interesting. I think regarding the FEV1 though, Patrick, to your point, I expect that providers who would consider these drugs and patients who would consider taking them would have a different threshold for what kind of FEV signal they would consider significant.

It's not going to be, you know, what we saw in the trials has a total because the populations have shifted and baseline care has shifted, baseline health status has shifted. If we are going to allow a somewhat less challenging path forward, I think it's reasonable to expect some convincing FEV signal if that's what we're going to hang our head on and a placebo control to be present, I think that's at least worth mentioning.

DR. FLUME: So we're going to run out of time to -- if we get the next ones, so Tim and then I want to bring up exacerbations.

DR. AKSAMIT: And if I could just ask Dr. Lim once again, so there was supporting data on the 2-3 percent improvement in FEV1, but a priority was to

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determine that a 2 percent or 3 percent change as a primary endpoint would suffice as is clinically significant endpoint going into the study?

DR. LIM: No, it was not. In our last --

DR. AKSAMIT: What was our percent that was a predetermined a priority going into that?

DR. LIM: In the DPARP, we don't really have a magic number, so no.

DR. FLUME: There was a power analysis done without doubt, but the -- can we just -- we have little bit more time to talk about exacerbations. We heard that there isn't a firm definition, there's multiple definitions being used, but there's time to event, there's frequency of event, this may become more relevant in our afternoon discussion, but does anyone comment about exacerbations as an endpoint? Maybe I could start with saying does the agency have problems with that in an open label comparator study?

DR. NAMBIAR: I think our biggest problem really has been the definition of exacerbation and the varying definitions used. So as long as the protocol specifies and it's only a doubt ahead of time, I don't

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think that per se would be a problem, but as was pointed out earlier is how many of these criteria that go into the definition of exacerbation are all subjective and what are the components of the definition, that's what's important.

MR. FOLLMANN: So in terms of exacerbation it seems to me looking at like multiple counts of exacerbation would be more statistically efficient than just using the first -- the time to first exacerbation and it sort of more meaningfully, I think, describes long-term behavior, the patient or the drugs, so I think you could count these as sort of recurrent events where recurrent exacerbations would seem to be preferred to just using time to first.

DR. AKSAMIT: And I can't comment for the CF cohort, but I would just share to add into this that when we did our retrospective analysis for the respire program looking at the definition of exacerbation using a less stringent definition, it did not have a positive impact on data. So there was a little bit of change in signal presented at a post-ready TS (ph) in May, but it didn't change the primary data or outcomes, it wouldn't

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have made the primary endpoints even with less stringent definitions so the -- although most of us think that sometimes if we liberalize the definition of exacerbation, we may actually find ourselves making endpoints when in fact at least our data from that study wouldn't support that.

DR. FLUME: So the endpoint used in maybe all of the CF trials that then an evidence of a change was actually physician decision to treat and I'll start with the very first one which was the Pulmozyme study which was where the Fuchs criteria came from and the definite -- the endpoint was actually IV antibiotics and the Fuchs criteria were only intended to validate that it was -- the antibiotics were for the treatment of respiratory complications. So it was never intended to be those criteria, those symptom lists was actually defining the event, it was the IV antibiotics.

MS. HAMBLETT: I have two comments. The first is I think for an exacerbation endpoint and an active comparator study that sort of gives me heartache, it makes me very nervous because I think that the effect size will be quite small and so an expectation that,

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you know, we're going to find a difference that would take a lot of patients on top of an active comparator for that endpoint. On the second, in response to Dean's comment, time to versus frequency, I would say it's complicated. From a statistical standpoint one would expect that you would have more power with recurrent events. I will say that that's not always the case.

We have seen that sometimes the effect size is a bit attenuated with frequency of exacerbations. In one of our CF trials of azithromycin, we have looked at the data both ways. And so doing, you know, recurrent event analysis versus time to, they're different. So if we use that data to plan a future trial, it's quite a difference in sample size, you know, in terms of which endpoint would be the primary endpoint. If time to is the endpoint we probably need a trial of about 300 patients in 6 months versus the rate. It's a harder endpoint to achieve, it's a little bit -- it could be harder to achieve. From a long-term clinical perspective, it made more clinical sense, but the sample size, you know, based on some of our data

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indicates we need a longer duration study and quite possibly more patients.

MR. FOLLMANN: So for that analysis, you could like analyze using time to first event and you get a P value and you could analyze using multiple events, recurrent events and get another P value and you're saying the P value was smaller for time to first event compared to you think recurrent events?

MS. HAMBLETT: The P value was larger using recurrent events.

MR. FOLLMANN: Right, okay.

MS. HAMBLETT: Yes, than as compared to a smaller more significant P value using time to event and the effect size was attenuated using recurrent events. So I just -- my point is just it's complicated.

DR. NAMBIAR: So I think in the interests of time, LaRee, you have a quick comment? Shrimant, you had some?

MS. TRACY: No, just a few on that. I mean you certainly can enrich your population to ensure that you observe an adequate amount of events and I can't

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speak to this as an expert, but in the cardiovascular arena they certainly look at time to recurrent event as an endpoint frequently, no pun intended on that, but often and then furthermore it's what -- it's not just peeled eyes (ph) where we want to model and analyze what's happening that the patient over the course of the clinical trial and that to me is what's most important is we're capturing every event or adequately accounting for those events as well as the time of the event.

DR. MISHRA: Yeah, just a very quick comment; I mean I think the open-label issue is, you know, something you can't completely discount. I think even whether you're using exacerbation definition or, you know, looking at whether a physician is going to treat because obviously I think those things can be influenced by knowing the treatment that you're on. I think, you know, if you have no choice but to do these trials, that's okay, but I think the burden then becomes sort of on the agency I guess to really look much more closely at the trial conduct and make sure there's not any sort of weird things popping up where

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you're seeing certain sites, you know, sort of doing things in tandem, and you know, making decisions where it looks like bias is influencing them. But as you think -- you know, again I don't think we can totally discount that. Open-label, you know, is not without its faults, but it's more just a feasibility thing, but I think it can influence, you know, the way that the trial is done.

DR. NAMBIAR: Let's just see, are there any comments?

MR. KADOORIE: I agree with Dr. Hamblett that in these active control trials that looking at an exacerbation endpoint is you don't have very much power. I don't think you should give up on that endpoint. I think what you can do is look at a pooled analysis across trials, you know, and have that as a requirement to see if they can meet that endpoint.

DR. NAMBIAR: Let's see, are there any questions or comments from the audience before we move on to the next session? No? So I think we'll move on in the interest of time to the next discussion which is around chronic MRSA infection in patients with cystic

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fibrosis. So Shrimant, I think it's your turn again.
Thank you.
OVERVIEW AND ISSUES:
DEVELOPING INHALATIONAL PRODUCTS FOR THE TREATMENT OF CHRONIC MRSA INFECTION IN CYSTIC FIBROSIS
DR. MISHRA: It's me again. Hopefully it's the last time you'll hear -- see me up here, but I'm just going to very briefly talk about again developing inhalational products for the treatment of chronic MRSA infection in cystic fibrosis. I think some of the issues -- or a lot of the issues actually overlap with, you know, what we've already been talking about, but there are some sort of unique features, you know, related to this indication. Just quickly saying the problem I think Dr. Nichols has already sort of discussed this beforehand; there is an increasing prevalence with staph aureus infection both, you know, with MSSA as well as in MRSA in CF patients is roughly a 70 percent prevalence for MSSA and 26 percent for MRSA. And you're seeing a transition that, you know, much, you know, with staph aureus in general to community-acquired MRSA in small colony variance which

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can be a little bit more difficult to treat and may be associated with biofilm development.
Generally, you see the highest rates in sort of the young -- the adolescent young adult population, so between 10 and 30 years old and I know there's, you know, some debate about this, but it seems as if there is some clinical data that suggests that chronic MRSA infection is associated with declines in pulmonary function, increases in mortality and less return to baseline post-exacerbation. A really important point is that, you know, how this is treated I think in the clinical setting from our understanding is pretty variable. There's some patients who are taking nebulized, you know, Vancomycin chronically, there are other patients who are only treated when they have an exacerbation, whether that's through a combination of systemic therapy with oral medications or a combination of oral and nebulized, but again there's quite a bit of diversity in how it's treated in the clinical setting.
So obviously a targeted inhaled therapy could be a benefit because it would act locally with less systemic exposure and if you have a drug with known

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safety properties, that's even better because you may be able to limit the systemic exposure. But again, you're also adding to the inhaled therapy burden of CF patients, so I think you really want to be sure of the benefit of the inhaled drug. So again, just to talk about some of the trials on considerations, I think we've discussed a lot of this already. I think placebo-controlled and in this setting a little bit different than what's been discussed with pseudomonas, obviously there are issues with ethics and feasibility and obviously the limits on the duration of the placebo trial, but it seems as if it may be a little bit more feasible from our understanding to do it just because there's a little bit -- there's not quite a standard of care out there yet in the clinical setting and there may be a lot patients who for, you know, this therapy is not standard. And obviously if you could do that trial, superiority could be more easily demonstrated and I think something that becomes important for us is that you would like to show definitive evidence of treatment for, you know, against a placebo before something become standard of care in the clinical

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setting and you don't really have a clear idea of what the benefit of this sort of standard of care comparator actually is.
I think the issue of choosing a comparator is inability to demonstrate superiority, establish non-inferiority margin, but again it may be easier to do the trial and for longer. I think it's already been mentioned, you know, the paradigm for all the CF trials is basically at this point to do 28-day on/off paradigm, but I think -- you know, so one thing we need to consider is should we look at continuous therapy, should we look at shorter cycles, shorter on/off cycles or do we need to really follow this 28-day on/off paradigm, especially when you're pursuing a different indication. And how can we enrich this population? Can we target subjects depending on the endpoint? Of course, that may limit generalizability.
So again, we've already discussed a lot of this, but the potential endpoints might be clinical whether using exacerbation, time to hospitalization, but again how do you define it and what's the study duration needed to capture the number of events with

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something like exacerbation is there and you need it all to connect that to long-term clinical data such as mortality data. Could you look at microbiologic endpoints in the case of eradication? If it's not eradication we're talking about, then what would be sort of a feasible definition of reduction, or is that even feasible at all? If we're going to look at biomarkers in circuits, you could look at FEV1 percent predictive.

Again, we've talked about what's a clinically relevant change, and you know, can we correlate that with long and short-term clinical improvement and of course PROs, you know, first we need our validated PROs really available and again what's a clinically relevant change.

Do we think that can stand alone as a primary endpoint if it's not supported by microbiologic or pulmonary function changes? And a lot of these issues with these definitions overlap, so just -- again just how do you define each of these endpoints. Some are obviously specific to the endpoint itself, especially when you're talking about the age of use for PROs or

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PFTs and some endpoints maybe best suited for particular groups such as mortality in adults with severe disease.

And just some final quick thoughts, obviously we can't address everything today, so I think some basic questions for considerations, I think, you know, what is the most value when you're looking at this indication for the particular patient population? What is their risk threshold in terms of the trials that they think that patients would be willing to participate and what kinds of data are they requesting? You know, do they just want short-term data or much more long-term data considering they're going to be on medication potentially for a very long time. So how do we ensure an adequate safety database and what's the biggest barriers for investigators in doing these trials? And again, it has been noted there is a lot of information in CF registry, so how do we leverage those registries, you know, to get the information we need? Thanks.

DR. NAMBIAR: Thank you Shrimant. Did we have Sunita (ph)? Did we have questions for this session?

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UNIDENTIFIED SPEAKER: No.

DR. NAMBIAR: Not specifically, okay. So you know, I can start the discussion, would be interested to hear thoughts from the panel. I think in contrast to what we've seen with chronic pseudomonas infections, I think our assessment has been that placebo-control trials are potentially doable. I think what we would like feedback from clinicians is, you know, is it -- are we still looking at maybe a shorter term like a one cycle or is this a patient population because there is no standard of care, we don't have approved therapies to treat their infections by inhaled route, you know, is it -- it's a doable, is it potentially feasible to do longer term studies? What might these studies look like and I think often we might have to also deal with co-infection because there is a fair number overlap between -- MRSA infection also having pseudomonas infection. So I would welcome thoughts from the panel and certainly lot of it overlaps with what we've discussed with regard to endpoints as well.

DR. FLUME: So I will start by saying that although staph was the bug that was introduced here,

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you could potentially take any of our bugs and insert them and ask the same questions, it works for pseudomonas, would have worked here. But the first question that's to be answered is what's the evidence that the bug is doing harm and then what's the evidence that treating that bug results in improvement? So you'd like to have greater confidence of that and that unfortunately takes time and effort as opposed to just assuming that, well, you have stenotrophomonas, therefore I must suppress it. And those are the steps that take time that have to do. What we have right now is registry data that demonstrates an association between worst outcomes and certain pathogens many of whom might take the blame because it might be the other bug that's present there. Nonetheless, staph is the one that has had the most attention, there have been eradication trials and there is ongoing suppression trial.

So just for your other question about feasibility, I think number 1 in this round, you absolutely have to have a placebo because there isn't a reliable comparator. Interestingly for staph and for

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some of the other bugs there are other oral agents unlike for pseudomonas, but I still do like the idea of avoiding systemic exposure so it's still a legitimate approach that you may have cheap oral therapy that would not meet the same standard.

You'd like to see durable response, not just the short one, but the other problem is in recruiting patients to a study. They like shorter studies. They like studies to start and finish and they also like the opportunity to be able to have access to the drug. So having open-label extensions is a very attractive aspect for those patients. So if you came in and said, well, we're going to do a 2-year study, I think we would -- we'd be failed before we can start it because that's just too long for people to want to be involved in a study like that. Six months became sort of the precedent because that's what was done with TOBI and case II was two cycles in an open label for third cycle I think or might have been three cycles on the active comparator, but that's sort of the precedent.

In terms of the decision about cyclic, it's the same complaint that we have with pseudomonas. I

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don't see the logic to a cyclic therapy, but that's just me.

MR. VANDEVANTER: Given the lack of natural history for these other bugs relative to pseudomonas, in fact these other bugs were the background when pseudomonas was shown to be a problem, many of these patients were staph carriers. I don't know how you can avoid asking sponsors to demonstrate a long-term benefit of suppression and I think the challenge the sponsors will tell you is that anecdotally we know there are patients now that really do benefit from staph suppression. These are patients that are almost impossible to enroll in long placebo control trials, so we end up enrolling patients that are culture-positive, but maybe not clinically in need.

And so it's similar to our challenge in pseudomonas in that we know who the patients are with the most unmet need, but those patients really can't afford to go off of their therapies in order for us to demonstrate benefit. So I think what you'll find is that there is a large population of patients with staph that could be involved in a placebo-controlled trial,

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but they probably are not in a clinical state where there's -- it's obvious that they would benefit and that's at the sponsors' risk to run those studies.

DR. NAMBIAR: I think we've also heard that in some institutions inhaled therapies are being offered for patients, you know, some drugs are being compounded and used, and so that is seen as an impediment to being able to enroll in these trials and I don't know how true that is, how prevalent such use might be across institutions, so would be interested in the outcomes.

MR. VANDEVANTER: It's certainly true a case that there's patients on inhaled vancomycin and they would not be for instance, for the -- a trial they wouldn't be good candidates to randomized off and I'm sure it's true at other institutions and it's a, you know, clinical decision that empiric observations that these patients tend to be stabilized if they're on some sort of anti-staph therapy. So that's the best indication that there may be a role for these drugs is the empiric observation, but those patients unfortunately are not good trial candidates.

DR. FLUME: But they might be not just on

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inhaled vancomycin, there's a fair amount of Bactrim, Doxycycline, clindamycin utilization out there. We don't track that in the registry, but they are being used.

MR. HAWKINS: Is the use of a compounded antibiotic recorded in the registry? I don't know if it is. And could that be used to help indicate a need or not a need?

DR. FLUME: Only if it's asked for. So we capture colistin which is non-approved product in the U.S. I don't know if we capture ceftazidime or other, it's just those three.

MR. HAWKINS: It seems like it would be useful to start asking them to ask for that as an aside. I mean, if it's -- people are using the whole list and we have this whole big registry, it sounds like it would be a good thing to capture.

MR. VANDEVANTER: So not so much excitement about the other bugs I guess. The -- that sort of alluded to identifying the patient population and so on the one hand if you use a marker, you have the bug, that may not be sufficient, so trying to define the

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patients who are most likely to benefit is that history of exacerbations treated for staph or --

MR. FOLLMANN: I had a question I guess it relates to inclusion criteria. So you mentioned that some of these patients are infected with the unusual bug like MRSA as well as pseudomonas. Do you restrict to just patients who are infected only -- who are not infected with pseudomonas or do you take all comers, some of that have implications for efficiency of the trial?

MR. VANDEVANTER: They are included and all comers because if you exclude them, your pool gets much smaller, so feasibility plummets. What is attempted is to synchronize. If they're on inhaled antibiotics targeting pseudomonas to try and understand how that fits into the measurements of the endpoints which is a challenge if they're not on cyclic therapy. And then, of course, to stratify across, you know, to stratify in your treatment arms.

DR. NICHOLS: Patrick, I think to your question about defining the patient population at -- to me the NTM model among these special pathogens (ph) may

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have a special place, not to use that word too much, but the point being I think we have more data, more evidence to suggest pathogenicity in response to treatment there and yet we still see a need when we're trying to develop studies around the NTM to have a unified approach to defining those who are just infected as opposed to those who have NTM pulmonary disease and need to be treated. And if a similar kind of approach could be taken to some of these other special pathogens, if you will, to define those as Dutch said who aren't just perhaps colonized or infected without clinical decline, I think that would be an important step forward.

MR. FOLLMANN: How can you -- what methods are there to distinguish between colonization of the special pathogens versus being causative of the disease?

DR. NICHOLS: It's a CFF-funded project being run out of Colorado right now, but basically applying the ATS criteria for pulmonary disease to the NTM population and there -- and we're finding about a third of our patients go on to develop disease. Just very

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briefly be a little more specific, those who are showing evidence of clinical decline which can be a greater rate of loss of lung function or exacerbation frequency and are not responding to treatment for their usual suspect pathogens, so they appear to be declining and we're treating them for everything but NTM and they're still declining. It's fairly loose, I appreciate that, but that's how it -- there's some radiology brought in, that's a little bit squishy in CF because of the background.

MR. VANDEVANTER: But as I mentioned earlier it's largely empiric observation that if you go after particular pathogen and you see patient improvement, you infer that that pathogen was involved in the process. It's indirect, but it's really the best data that's available at the patient level.

DR. FLUME: And we recognize that we use macrolides in our patients, in patients who have pseudomonas knowing full well that that's perhaps not the target. But I think since we had a little of silence there, I'd like to shift to the one question that didn't get looked up, but the one question that

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didn't get addressed because it might be highly relevant for this afternoon's conversation and that's the safety issues. We can talk a little bit about resistance, but Anne?

DR. O'DONNEL: Yeah, I mean I was going to ask again, you don't know from your registry how many patients are being treated chronically for staph? I mean, you said something like 26 percent have Staph?

MR. VANDEVANTER: I think the answer is we don't confidently know that.

DR. FLUME: I don't think we capture that. It's pretty large registry, so anything we add to the registry, we have to find something we can subtract.

MS. O'DONNEL: And I was going to ask about resistance, because you CF people think it doesn't matter and we haven't really talked about that yet, so.

DR. FLUME: So just so you know I have feet in the bronchiectasis camp as well. Maybe as an introduction to this section, I just want to tell you about an ongoing project.

The -- and it came from discussions with the bronchiectasis community. And in fact, Tim was the one

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that asked the question or maybe he requested something. But it was about we keep talking that the resistance doesn't matter and we never say it in public or won't put it in publication.

And so we have a project that's been funded by the CF Foundation, The European CF Society, UK Trust, CF Canada and CF Australia to pull together clinicians, pediatricians, internist, pulmonologist, infectious disease pharmacists, microbiologists to address the issues, and there is a five-pronged approach.

The first of which has already been submitted for publication. That's just establishing definitions so we know what we're talking about when we say resistance and the inadequacy, if you will, of the methodologies used to culture bugs and so -- and know about susceptibility.

The second prong actually is led by Dutch, is a systematic review of the literature that -- to identify what is the prognostic value of microbiologic data with clinical outcomes. So we recognize there's a discordance between susceptibility, test results and outcomes.

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The third is the Delphi approach with this group trying to come to some consensus about statements that can be made about how to use the microbiologic testing.

The fourth is an engagement with the antimicrobial stewardship community. They have basically stayed away from the CF world, but we need to find common ground so that -- the issue is not whether you shouldn't use antibiotics, it's how best to use antibiotics.

And then the final piece is about the communication of all this, the education for patients, for families, for industry, for clinicians, for the agencies to try to -- how do we share that information.

So the first piece is already completed and it will get up for publication. The next two pieces will be finalized in September and then we will begin the programs in October, going public with the rest of the information.

So it's trying to at least establish the current state of knowledge of what we know about response to treatment and microbiological data.

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So with that -- there is a discordance between clinical outcomes and microbiological data. And people often want to go to the culture results to help them have guidance in terms of how to manage it.

And a common story will be, well, when I change the antibiotics the patient tends to do better, so it's got to be a resistance issue to which I would reply. Sure.

The question is how did your culture result inform you of that? Because it's equally likely that that bug was resistant to the drug you were using or susceptible to the drug you've used, but now resistant to the one that you're choosing to use. Or your patient responded to a drug in which the bug that you identified was already resistant.

So it's a much more complex issue than dealing with, say, a pneumonia where you may have a clonal organism that is planktonic and responds well to the antibiotics that you use. But in CF, the experience is very different.

And issues that were raised at the recent AD Panels regarding susceptibility and fear of selection

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of resistance we sort of lived with 20 years ago. And the reality is 75 percent of the eligible patients are still on inhaled tobramycin. IV tobramycin is still the most common used medication in the treatment of exacerbations. So it's okay to be fearful of it, but the empiric observations are that it hasn't been an issue.

MS. O'DONNEL: Then, for example, why is anybody on Colistin with CF.

DR. FLUME: Well, first --

MS. O'DONNEL: If that's like your backup drug. I mean, is it because the bugs are resis -- turn resistant or it's just a clinical decision in CF?

DR. FLUME: So typically antibiotics are chosen because patients didn't respond to something else or they couldn't tolerate it. So it's the rare circumstance, at least in the U.S., that Colistin will be the first drug chosen.

I can also -- and I can invite Dutch to comment on this that what you get in the culture isn't necessarily what you're using in the person and notions of no resistance for Colistin is sort of farfetched.

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MR. VANDEVANTER: So I have to say coming from case, it also depends on where you were trained, whether you use Colistin or not. So Cleveland is notorious for Colistin use and it's not necessarily objective medicine. It's just the way people were trained.

I think it's important when we're having this discussion to just discriminate between resistance for inhaled antibiotics where this is a topical treatment and we know that parenteral breakpoints or systemic breakpoints are really not relevant.

The concern is, is that we will create organisms using this topical therapy that then will be recalcitrant to treatment with systemic therapy. And again, what we know from when we use systemic therapies in these chronic pulmonary infections, whether it be non-CFBE or CF.

We're treating a pulmonary exacerbation where our goal is not to eradicate the organism. It's to -- it's basically a palliative treatment to get patients symptoms reduced and to get them back to their normal baseline.

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We know and we do publish occasionally, Tim, that susceptibility testing really is not predictive of response either way. So patients can have susceptible organisms by culture and not respond to a certain therapy and vice versa.

I think the important precedent is to look at Tobramycin, which at the time that TOBI was approved, was the cornerstone inhaled antibiotic -- I mean, IV antibiotic for treatment of pulmonary exacerbations. 20 years later, still 70 percent of patients on inhaled Tobramycin and Tobramycin continues to be cornerstone IV treatment for pulmonary exacerbation.

So I don't mean to imply that there is no selection for reduced susceptibility in that population, there has to be, because we're giving antibiotics and we're not eliminating organisms. But what hasn't happened is we haven't lost the ability to use these classes as systemic therapies.

And as far as I can tell we've seen the same thing with Aztreonam. Aztreonam wasn't necessarily as useful as an IV treatment before it was approved as an inhaled drug, but I don't know that it's gotten

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particularly less useful since.

And I think we just need to accept that traditional in vitro susceptibility testing is just -- it's no more useful than an X-ray for determining whether a patient is going to respond or not and that's the reality of the situation.

DR. MISHRA: Sorry. Can I just ask a very quick silly question maybe? So when you're talking about nonresponse, I mean what does that patient look like? Is that a patient whose pulmonary function is essentially remaining stable and they also are not showing any sort of reduction in their colony counts when it comes to the organism or how are you guys defining that? I'm just trying to --

MR. VANDEVANTER: So I will say that colony counts are irrelevant. It's -- whatever the clinical presentation was that dictated that there'd be intervention that tends to be the -- does tend to be the response elements that clinicians are looking for.

And often what will happen is a susceptibility test will go in at the time of admission to hospital and they won't get those results for five or six days.

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And during those five or six days the clinician knows full well whether the patient is responding to the treatment or not.

And so, if they're not responding then they can look at that micro result and say, oh aha. But often what happens is, is the patient's responding, they ignore that. And so it really is -- and I defer to Dr. Flume and other clinicians.

But it's pretty evident within four or five days that you have symptom reduction and that -- this is a patient you've worked with again and again and again. You have a -- there's a patient/physician dyad there. And so it's pretty clear when response has happened and that response tends to be irrespective of the micro results.

DR. FLUME: So we would respond to a variety of signals actually in publication now is those patients whose lung function drops precipitously and nothing is done. And now we know better that those patients do poorly, later on they lose their lung function.

So hopefully we'll see greater intervention

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based on FEV1 alone. These are generally people with very high functioning BFTs.

But even if your patient doesn't have a change in lung function, but they're telling you, doc I don't feel well. We hear that and we look to do something to make them feel better.

And we're trying to struggle with is it a need for an antibiotic or is it a need for an anti-inflammatory or would airway clearance be the ticket there to try to figure out what they are needing? And if you're not having success with something you're looking for something else. So we're hopefully highly responsive to what patients tell us.

DR. ZEITLIN: To that end -- and I risk you're being upset with me. But we often find fungus as an ideology in pediatric CF and that complicates the response. And I know you didn't want to talk about that.

DR. FLUME: Yeah, the fungi are a whole another subject and they're in that sort of entity that historically people thought Canada means nothing. Aspergillus, you got some people that think it's a

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culprit and others haven't found a benefit even treating patients that demonstrated.

And then you've got all the other fungi, we're finding like Scedosporium others that people are worried about. But they're sort of parked in that same thing, like well what's the evidence for Steno and Achromobacter and others.

MS. O'DONNEL: I mean I know we're going to talk more this afternoon, but this has been the bugaboo in -- from the FDA's point of view, at least part of it -- right -- the development of resistance.

So I know we clinicians do what you say, but how we're going to show this in a trial that it's safe if the bug becomes resistant? I mean, that's your -- part of the FDA's concern and is the ADCOM concern.

DR. FLUME: So, I'll --

DR. ALLENDE: I just wanted to -- talking about resistance, in the last Advisory Committee we received important feedback regarding this as a broader impact. And they asked us to monitor the colonization of non-respiratory sites, for example, the gastrointestinal tract because of the impact on future

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infections and also for reducing the number of treatment options for those other infections that patients might have and be colonized with.

For example, the NTM colonization and the continuous exposure and what happens with the non-respiratory sites as a potential risks to monitor. That was a concrete advice we had for future trials.

DR. FLUME: That was from infectious disease docs without any doubt. The challenge -- we understand the fear, right. You just don't know -- you don't know. But you have to pay attention to your empiric observations, the realities of what's going on.

The first question one should ask is what is the evidence that resistance is bad? Now if your bug is causing disease and you don't have a drug to treat it, then we will agree that it's a bad thing.

But resistance is the interaction between a drug and a bug. Virulence is the interaction between a bug and a person. And so you could, and we frequently do have highly resistant pathogens which are slugs (phonetic 3:01:44), they're not doing much of anything.

And so, although Time and Newsweek can put

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resistance on the front cover and say that is a horrible thing. That doesn't mean that's the issue.

And the other part is, we're focusing on a select population and ignoring issues like the agricultural use of antibiotics and the big global picture.

DR. COX: Yeah. So maybe just to sort of expand that a little bit. At least there's a couple of different things that I think you're mentioning, Patrick.

One is that you have a resistant organism that's not a pathogens, so maybe you've got to colonizer, right. Because if it's highly resistant and your antibiotic doesn't work against it, but it doesn't matter because it's not causing a problem.

I mean if it's truly a virulent organism and it's resistant and it doesn't respond to your antibiotic, than if it's really causing something and it really is a problem that the antibiotic isn't anything than you're not treating the condition that is a problem.

So it may just be that you've got a hodgepodge

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of different organisms, some of which are resistant, some of which you're finding, some of which you are not and it's a little bit in the dark and you don't quite know what's going on, and that's what's making it challenging.

Because I do have to respond to the comment, that resistance is a problem. We see patients out there that have resistant organisms, who have few treatment choices left. No doubt that there is a mixture of different organisms there and what role any one particular organism is playing in a particular patient at a particular infection can be hard to sort out. But resistance is an issue. If we lose the effective antibiotics, we sort of know where we are.

DR. FLUME: And I'm not going to be so facetious to saying I don't care about resistance. That the -- but a slide -- chronic infection is not merely just CF it's going to be important in the bronchiectasis discussion.

The -- we know now from microbiome analyses that this is a complex community of organisms. And the slide I used is from Where's Waldo?, where you've got

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all these people on there and you don't know which ones are the bad guys. And what you get in culture is some of that information. And the issue is how is that information informing you about the care of your patients.

So the general assumption is that if I put a patient on chronic suppressive antibiotics and I get a resistant bug then I've done something bad. I would argue actually it's just demonstrating that your antibiotic is doing what you asked it to do, because you've perhaps taken care of those that are at greater risk. The only bug that should be left -- right -- should be relatively resistant to your bug.

But the most amazing thing is that we've had TOBI, what for 20 years and we don't have 95 percent resistance. And so that's why I say we have to focus on the empiric observations and not just make the assumption that a resistance in my culture is doomed for my patients, my CF population or for that matter the community that surrounds them, because I'm not aware of any outbreaks of multidrug resistant pseudomonas in hospitals that have CF centers.

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MR. VANDEVANTER: I just want to say that resistance is bad, I'm there with you. But the problem is a semantic one that we talk about resistance and we're referring to an isolate with an R and we say that's resistant.

And I think what we're trying to say is that all kinds of CF patients have isolates with Rs, but they're not refractory to treatment. And they don't seem to be getting infections in other sites. And they don't seem to be contributing to community outbreaks of resistant organisms, so they are their own microcosm internally.

And it may be that by antibiotic classes some antibiotics do reduce virulence in association with resistance and that may be the Macrolides (phonetic 3:05:43) claim to fame.

But where we get -- where we run into problems is when we talk about, when we conflate Rs and Ss with the little R, resistance. And that's what I've seen in AD panels is this concern that we've looked for a year and what we see is that the number of Rs continues to go up. So, therefore, at some point we have a problem

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and we need to extend these trials out for longer and longer.

And we're asking -- we're using a measure that doesn't provide insight into the clinical situation. It's not useful for the clinicians. And so of course we will collect it. But it cannot be used to determine a risk associated with the drugs in that patient population. It just cannot.

DR. COX: And just on the breakpoint issue. I mean -- the breakpoints are designed for systemic therapy which -- compared to local maybe different. But -- I mean, it does seem -- I understand your point. You're not seeing the issue. But I mean it does seem that ideally you wouldn't want to have more colonization with resistant organisms than not.

I mean, at some point if those things do sneak into the bloodstream and you're using a systemic antibiotic to treat them, if they're resistant, I mean the expectation would be is that you're going to have a higher likelihood of failure.

MR. VANDEVANTER: Yeah. But we don't -- these bugs -- we don't see bacteremias in these patients.

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DR. COX: So if you're not seeing the bacteremias that's a different -- then you're not going to have a disease. But if there should be an infection that would occur, you would expect that that would be -- if you have resistance in particular organism and using a systemic drug, it's going to be tougher to treat those patients.

MR. VANDEVANTER: It's true. But I think you need to step back and look at the risk-benefit of a population that's now doubled its median predicted survival. And we -- I guess it's a risk we've been willing to take.

DR. COX: Yeah. No question there's a risk-benefit. If you're -- if there's a very low frequency of disease condition that you're going to have more difficulty treating and there's clear benefit from using, yeah, than it's a benefit risk that would be in the favor of treating, no question.

And the reason I'm responding is probably just because I do think resistance matters and that's what I thought was important to put it in the equation.

DR. NICHOLS: Can I -- I just wanted to ask,

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because I struggled with this too like you've heard from the other clinicians, because of this lack of association between resistance and clinical outcomes.

So in my view resistance is an indicator that your drugs should no longer work. And in CF we've demonstrated now for two decades that the drugs do continue to work when given inhaled and when given systemically.

The other risk may extend to the community of risk spreading contagion with resistant bugs to the community. But I don't see any evidence of that.

And so sincerely I would like to hear in the context of CF in inhaled and a microbial therapy where is the focus of that risk? Is it developing new drugs that may not follow same pattern we've seen over the last two decades or is it more a philosophical concern with increasing the MICs?

DR. COX: So I understand the issue of -- you can continue to treat, you continue to see benefit, but at some point, it would seem that you would get to a point where your antibiotic would not work.

I mean if the organism is resistant that by

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definition means it's not responding to the antibiotic. The antibiotic is not active.

So the breakpoints that you may be looking at on the lab reports are probably those that are designed for systemic therapy. So what's going on in the lung may be more complex and it -- and the levels that are attained there may be completely different than what you get with systemically available therapy.

I mean as a basic principle, if the antibiotic is not active, you're not going to expect a clinical response. You're saying that -- I mean that is almost by definition. You're saying that you're still seeing a response which suggests that the antibiotic is still active.

If you think that the antibiotic isn't active against an organism that's completely resistant then I think if you asked yourself the question of, is this an antibacterial drug in this setting?

MR. VANDEVANTER: And so -- but what -- the problem with that construct is you take an isolate from a polymicrobial, polyclonal population and you read the MIC and you say, ah, this characterizes the infection.

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And what we know is that it doesn't.

So I'm not talking about inhaled antibiotics. I'm talking about systemic treatment of pulmonary exacerbations where the Rs and Ss just do not predict -- S doesn't predict response any more than R predicts lack of response. It just doesn't in that setting.

And it's about the test. It's not about whether -- I agree with you. The point that you populate the lung with resistant organisms, it's no different than populating them with an intrinsically resistant organism. Yeah, you're not going to have an effect.

But the challenge here is we conflate doing a standard micro measure that works very well for bacteremia, for urinary tract infection, highly efficient. CLSI has this all figured out and we think that that extends over the treatment of pulmonary exacerbations -- it just doesn't.

DR. COX: And that's fair. And I think we've made this point a little bit earlier on, which you may not be culturing the actual pathogen that's causing the problem. What is actually the cause of the patient

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tissue? What's the virulent organism?

And I think if you think about this little bit more and try and tie it into the discussion that we started with, it argues pretty strongly for having good clinical endpoints, because absent good clinical endpoints it may be hard to figure out whether we're actually benefiting patients or not.

And empiric observation, I think, can be helpful when it's an event that you just simply would never see. But in settings where those differences are more -- they're not that large or there is variability, it really does argue again for well controlled trials.

So -- and it's really important -- I mean, we have seen instances where well controlled trials are not done and the field kind of gets beyond the well-controlled trials. And you don't really know the basis for what you're doing.

And it can be -- it cannot be good for patients, because you don't really know exactly what you're doing. It gets adopted, it become standard of care and it becomes difficult for new therapies to develop, that may truly help patients. You may be

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doing some things that don't actually provide benefit to patients. So it really is important.

And this is not a criticism of the CF field. I mean, we've seen this in a variety of different fields and so it really argues for the importance of well controlled trials for really -- for benefiting patients, so.

MR. VANDEVANTER: I mean, part of our problem at CF is that we have a lot of that that's going on that now is our standard of care. So if we're using active comparators, it's very difficult to know what -- if there is efficacy with those. I agree.

DR. COX: And a very fair point. And we're all human beings, we all want to do something to help immediately and it really is important and I appreciate your comment, your willingness to actually say it that sometimes we get a little bit ahead of ourselves and we don't really know where we are and that's not the best situation for patients, so appreciate your honesty.

DR. AKSAMIT: As the accused instigator of this -- at least for the non-CF group, I would also say in for the record that resistance does matter on the

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other hand, like my other colleagues. But you're all wrong kind of thing, is how that goes.

I would like to expand on just a couple of points. The first is not to overstate the importance of longitudinal analysis and whether that's an acute, subacute setting or more chronic setting about what the specific pathogens are.

And we wrestle with this all the time, whether it's pseudomonas, staph, fungi or the NTM that we do need to take this in the context of clinical symptoms in addition to other components of the data, whether it's a definition for NTM pulmonary disease or otherwise.

We need -- sometimes need several days before we can determine, I think that this is an operative pathogen or a need a month or I need three months or six months for NTM disease sometimes in that situation. So longitudinal is analysis of important.

Having said that, if we start thinking about this impact more long-term on this diversity, community of organisms, I think, to address your concern about what happens in other sectors, this would be best

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served in a formal post marketing analysis requirement. Because right now none of this monitoring is being done and this would be a great opportunity for us to move forward and inform ourselves are there signals arising that we should take note of.

And again, along your line of rationale that are markers that maybe we are creating problems and you say, well, how best to do that. And it probably would be best served to do that in post marketing analysis.

And I think then we think about this in the context of this diversity of products and of organisms in communities with the microbiome and all the other factors that go in.

And so as was mentioned is, is that single organism that's isolated on a micro report really reflective of that phenotypic presentation of what's going on with the patient. And the PCR microbiome analysis would suggest probably not it's an oversimplification of a lot of things going on.

So we have to think in when you say resistance is that necessarily correlate with what's going on phenotypically with that patient. They may or may not

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when it's a bacteremia, for sure, when it's pneumonia with a very monoclonal population, for sure.

But for bronchiectasis in this group of this diversity of organisms -- and anything we and you have to get down to the boxes many of you you've heard me kind of promote is to think about this in broader terms.

We may get to the point where we have inhaled organisms to repopulate diversities of organisms. Who would have think that you'd do a fecal transplant to help a person for C. difficile, for example and it can be a very effective strategy?

So, I mean, the point I just want to share is that we have to think about out of the box. And along I think both of your points, more in common than dissimilar, that it's not just necessarily about a single organism in a single event with a single R or S on it that really then translates into what's going on with the patient and he has an impact, as Chip says, on how they feel. So it just raises all those all-important complicated issues. Thank you.

DR. FLUME: All right. With that, I'm going

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to let Chip have one more word and then we're going to close it down for lunch.

DR. FROEHLICH: Thank you, Patrick. I wanted to share a perspective from a drug development point of view as well. Talking about resistance is very important and this is very important to us as well.

What I think we should discuss what is the right balance between the clinical data that you observe and then potential risk of resistance and when would or should a new inhaled antibiotic made available for therapy, but we see appropriate post marketing measures to test long-term safety and resistance development.

For me it's difficult to understand why you would refrain from making a drug available because you are concerned what might happen five, ten years down the road in the patient. And I think this is better served, as Tim said, in an appropriate, well controlled post marketing setting.

DR. FLUME: All right. Thank you. And with that, we'll close this session and break for lunch and then reconvene at 1:00 o'clock for the afternoon

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session.

LUNCH

DR. SMITH: Okay, we're going to start this afternoon with some formal public comments. We have three speakers. They each are going to have roughly five minutes or so for their comments. And we'll take them in the order that they're presented in the agenda. So if I could ask Amy Leitman please to come to the podium.

FORMAL PUBLIC COMMENTS

MS. LEITMAN: Good afternoon and thank you for the opportunity to address everyone here today. My name is Amy Leitman. I'm the director of Policy and Advocacy for NTM Info and Research, a non-profit patient advocacy organization for those with pulmonary tuberculos mycobacterial -- nontuberculous mycobacterial disease. I'm also the stepdaughter of a courageous and loving bronchiectasis patient who died only a few years ago from complications of her disease.

In my job, I speak from two vantage points, that of a patient advocate and that of a surviving child and caregiver of a patient. I've had the benefit

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of learning from personal experience as well as from the patients and leading experts in this field, several of whom are participants in this workshop today. Many patients I've had the privilege of helping have had serious pulmonary infections such as pseudomonas. These patients cannot be placed in silos. They may have pulmonary infections, but the root cause of the problem is their underlying pulmonary disease.

This includes my late stepmom, Fern Leitman. Though she also had NTM lung disease later in life, she spent most of her life as a bronchiectasis patient, starting at the age of 14 after suffering an episode of hemoptysis.

In the 32 years that she was my parent, she was on antibiotics many times due to exacerbations with pseudomonas in particular. This cruel and vicious cycle would repeat itself for 54 years before her kidneys finally failed from nearly a lifetime of systemic antibiotic use to combat the infections she had because of her bronchiectasis. She was one of those patients with a significant unmet need who could have benefited from better therapies.

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She personally told you about this 6 years ago at an FDA workshop on issues in the design of clinical trials for antibacterial drugs for the treatment of non-CF bronchiectasis. She pointed out that you treat the patient, not the test result, to underscore the importance of designing clinical trials in a way that will have meaningful impact in real world clinical settings. It's increasingly obvious that the clinical trial design paradigm doesn't easily apply to bronchiectasis patients.

In the ongoing discussion about the length of clinical trials, drug resistance is a subject that keeps coming up. Clinical trials should last as long as -- should last long enough to evaluate both safety and efficacy. But given that pre-trial safety studies are also conducted to suggest building a longer trial to evaluate drug resistance is neither useful nor ethical. The issue of addressing the long-term development of resistance would be better served with post-marketing analysis using structured monitoring that currently does not exist. To enforce a prospective requirement on clinical trials already in

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progress or concluded brings drug development grinding to a halt.

There is a practical consideration to this as well. Nearly half of all Phase 2 protocol amendments are avoidable and one-quarter of those are due to recruitment difficulty or feedback from sites and investigators. Protocol amendments are costly, averaging half a million dollars and a 3-month delay.

In the real world when a non-CF bronchiectasis patient is sick, they receive treatment with systemic antibiotics and off-label use of inhaled antibiotics. Well-trained clinicians will not stop treating them regardless of concerns over eventually developing drug resistance.

Or as one of the patient panelist from our Bronchiectasis Research Consortium said: "Don't plan a clinical trial design that you won't approve of once the trial is completed."

Forcing patients to endure excessively longer trials when it is unclear they are -- when it is clear they are the least able to participate in them is unethical. It puts physicians in the untenable

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position of either recommending a patient enroll a clinical trial, which may see them on a placebo for 2 years, which is 2 more years of damage and destruction to their lungs, or to advise against it because of the risk of 2 years of placebo, making it virtually impossible to enroll for such a clinical trial. Let me put it to you in another way. My stepmom, Fern, spoke at the FDA Workshop in September of 2012. She died in October of 2014. And that is the difference that 2 years can make.

The FDA's Patient-Focused Drug Development, PFDD, program may also significantly impact clinical trial design for bronchiectasis patients. Two weeks ago, the FDA issued its draft of the first of four methodological PFDD guidance documents for industry, FDA staff and other stakeholders. The document outlines methodology for collecting patient experience data as defined and codified under federal law.

Within the list of measurable patient experience data is, among other things, the burden of participating in clinical studies. This should include more than just practical day to day burdens. To

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properly assess whether the correct endpoints are ultimately used in a clinical trial, patient concerns should be heard and incorporated into clinical trials from the beginning when they are designed. If the clinical trial endpoints do not ultimately yield the product which addresses patient concerns, then neither the study nor the product hold as much value for the patient.

The draft guidance also addresses sample size. The FDA recommends that if the sample size is limited due to practical considerations, e.g., rare diseases, the research objectives should be adjusted accordingly.

I'm not sure how this can be practically achieved. Regardless of patient population size, if there is information about those patients that needs to be gathered, then we still need the data whether it's from 20 patients out of a total of 250 or 1,000 patients out of a total of 100,000.

The challenges that arise in rare disease population studies also impact sampling frame. In the case of bronchiectasis, not all doctors are created equal. There is a select group of physicians who

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specialize in treating these patients. They are frankly better at it than many of their colleagues and patients tend to gravitate to them. This clustering effect may also have an impact on random sampling, but it does not necessarily follow that this renders the study less accurate for this patient population.

I thank the FDA for convening this workshop. It's an important step forward in determining the challenges associated with designing clinical trials for what has repeatedly been described as a heterogeneous population and exploring possible solutions for that. We all benefit from the opinions and expertise of other.

It's my hope that everything we learn today will help design a roadmap for clinical trials that can accelerate effective drug development. This is progress that Fern advocated for and that so many other bronchiectasis patients needed prior to their deaths and it is progress that will help countless others facing this long and difficult journey.

I'd like to leave you with one more thought. I mentioned earlier that patients cannot be placed in

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silos, categorized as one disease state only. Comorbidities play an enormous part in defining the scope and nature of illness and this is particularly true of bronchiectasis patients.

When the FDA evaluates any new product using the benefit-risk assessment utilized in the PFDD program, doing so with patient input in order to more specifically calibrate the benefit-risk assessment will ultimately help lead to patient-focused drug development that fits within the agency's framework and yields better products for patients.

These are new frontiers for everyone, regulators and industry, patients and advocates, providers and researchers. It's a steep learning curve, and this is a benefit because it means we are moving forward, which is how we innovate. Thank you.

DR. SMITH: Thank you, Ms. Leitman. Now we'll have Mary Kitlowski come to the podium please.

MS. KITLOWSKI: Hi. My name is Mary Kitlowski and I'm from Loch Hill, Maryland. I have bronchiectasis as a result of a rare disease called primary ciliary dyskinesia or PCD.

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I'm speaking today because I -- because having studies that properly assess the efficacy of treatments and encourages the research and treatments of bronchiectasis is very important to me.

I've been frustrated by the continued failure of non-CF bronchiectasis studies, especially having taken part in some of these trials and experiencing un-improvement. I believe that the majority of these studies have failed in part due to several factors. The first is the heterogeneous nature of non-CF bronchiectasis. This includes not just the etiology of non-CF bronchiectasis, but also the prescribed treatments.

So the first slide shows a wide range of causes for non-CF bronchiectasis. There are so many unrelated causes, yet trials are created to treat them all the same.

The next slide shows how these trials are set up. As we can see from this analogy, tests in CF patients are performed on like subjects -- I know there are some differences, but very similar -- whereas non-CF bronchiectasis trials are set up on everybody else

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with bronchiectasis. So to me this is like having a trial: "Will a baseball bat consistently hit a baseball past the infield?" And then for non-CF: "Will a baseball bat consistently hit every other style of ball past the infield?"

When we look at the patients that are enrolled in these trials, we can see that the CF trials are fairly similar. Whereas with the non-CF bronchiectasis, we're not sure what percentage of patients with the different etiologies are going to be included.

Now you might think that this trial would have succeeded based on the last slide because we have softball and a tennis ball in here. But if you look at the actual participants, no tennis ball signed up for this trial.

This is a poster showing -- comparing -- from the bronchiectasis registry looking at different disease groups, primary ciliary dyskinesia being one of them. And the conclusion -- sorry; I learned how to use this. So the conclusion over here states that patients with PCD within the BRR are more significantly

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younger and that's by 30-plus years, more often report having respiratory symptoms, exacerbations and hospitalizations compared to the other groups.

So this is just an example of how these different disease groups within the bronchiectasis community -- we're not sure how that affects the overall studies that are being set up. And there are other differences that are not taken into account here.

In this slide again instead of saying that these are the different types of disease groups, we could even say these are the different patients -- the treatments the patients are on. We don't know if all the patients are doing airway clearance, what type of airway clearance that they use, are there other drugs that they are on for the other diseases that they might have. And we don't know how this affects the outcome of the study.

So the second issue is the rigidity of the endpoint set up for these trials. Unproven endpoints continue to be used as well as improperly applying data analysis to endpoints that misrepresent the endpoint as failing. The primary endpoint time to first

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exacerbation would not be a proper endpoint for me. I always have an exacerbation in the fall and this is not uncommon for non-CF bronchiectasis patients. At certain times of the year we retreat from society because that's when we are the most susceptible.

There's also a problem with how The Quality of Life-Bronchiectasis is evaluated, in particular in the Aradigm study when determining that the quality of life endpoint failed.

According to The Quality of Life-Bronchiectasis expert, Dr. Quittner, the endpoint was improperly determined using only the first quality of life survey before the patient started on the drug compared with the last one after they've been off the drug for 28 days. The survey only asked for a recall of 7 days. So both of these surveys were comparing the patients when they were off the drug. So a few slides from the Aradigm trial, and this was just to show how the QOL-B was used.

Now, Dr. Quittner was asked how to set up these survey -- you know, how the survey should be used throughout the trial. He actually was not asked how

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they should be evaluated. So in evaluating just the first one and the last one, you can see that the patients did 14 other surveys or 14 total surveys. So 12 surveys were not used in determining whether the quality of life improved.

So to me using the first and the last is like a cholesterol trial, where you test the patients' cholesterol levels before the drug is administered. Then you test the cholesterol levels again several months after they've had the last dose and determine the drug to have failed because the cholesterol levels have gone back up to where they were before they started the trial, despite evidence that their cholesterol levels had dropped while they were on the drug.

So a quick look. Again, this is one of the Aradigm slides. If you look along the vertical axis, that shows the quality of life survey. And you can see that while the patients were on the drug, they all said that their quality of life was better, versus down here when they were off the drug and the quality of life went down. Yet for the trial only two endpoints when

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the patients were not on the drugs.

Frankly saying that the quality of life endpoint failed in this trial, I think is misleading. And since an expert was not used in how to quantitatively analyze this data -- and I think this misrepresents to the patients. And I think frankly having them do the survey 14 times and not even looking at the other surveys was a waste of the patients' time.

Quality of life should be a primary endpoint and it should be used correctly. If these trials have shown anything, it is that we don't know what a good qualitative measure is for these trials. If patients are feeling better while on the medication, shouldn't that account for something, even if we can't figure out why?

My concern is that these continued failures without flexibility and adjustment to the set up and endpoints will deter patients from enrolling in these studies, and more importantly, discourage companies from putting resources into bronchiectasis research. Thank you for your time.

DR. SMITH: Thank you. The final public

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speaker will be Cara Pasquale.

MS. PASQUALE: Hi. My name is Cara Pasquale and I'm speaking today on behalf of the COPD Foundation, a non-profit organization with a mission to prevent and cure COPD. The foundation also provides research, education and support for the bronchiectasis community, a closely related lung disease and a common comorbidity of COPD.

The foundation started and operates a bronchiectasis and NTM registry, a consolidated database of non-CF bronchiectasis and/or NTM patients to support collaborative research and assist in the planning of multi-center clinical trials for the treatment of these diseases.

We are grateful to the FDA for convening today's workshop to discuss inhaled antibiotics for non-CF bronchiectasis. There is significant unmet need in the patient population and the recent Antimicrobial Advisory Committee reviews of treatments indicated for those with non-CF bronchiectasis with the presence of pseudomonas were met with optimism and excitement in the patient community.

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Understandably, the decision to not approve either application was met with disappointment in fear of what comes next, especially for those with severe disease who have few other places to turn for hope.

For these reasons, the discussions taking place here today are critical to the patient community, recognizing that the FDA's mission to ensure the safety and efficacy of new treatments is of the utmost importance.

We would also like to stress the importance of considering the needs, priorities and preferences of the patient community as discussions move forward.

We understand there are questions regarding the most appropriate outcome to use as primary and secondary endpoints in pivotal clinical trials. The most recent examples of inhaled cipro have been measured based on whether or not the drug improved the time to first exacerbation after the patient started the drug. This outcome may not adequately reflect if patients truly do and feel better on the new treatment as there are many treatments which can influence this outcome such as existing off-label antibiotic use,

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presence of other comorbid conditions, exposures in the patient's daily life, exacerbation risk factors and more.

We partnered with the NTM Info and Research to better understand the outcomes that patients prioritize. In a preliminary survey following the recent Advisory Committee Meetings, 284 patients ranked frequency of exacerbations as the second highest priority outcome, closely behind overall lung function, something highly impacted by the frequency of exacerbations. In a follow-up survey, quality of life was ranked first by a small margin over frequency of exacerbations. In each instance, time to first exacerbation was by far the lowest ranked priority.

Patients ultimately want to feel better and these surveys have demonstrated that the most important indicators of this are how they are breathing and living, whether or not they are avoiding the frequent flare-ups.

In addition to issues regarding the most appropriate outcome, there has been a great deal of discussion surrounding the most appropriate length of

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clinical trials in non-CF bronchiectasis, with some suggesting that trials should be a minimum of 2 years or more in an effort to determine if the treatment effect is reduced over time or if antibiotic resistance becomes a more significant issue.

In the most recent patient survey, only 22 percent of patients said they would be willing to participate in a trial that involved the chance of receiving a placebo medication for 2 years and about 25 percent of patients indicated they would not participate in any trial involving a placebo medication regardless of the trial length. About 56 percent of patients selected they would be willing to participate in a trial with placebo if the trial length was 12 months or less.

It is known that non-CF bronchiectasis patients who have frequent exacerbations consume heavy doses of oral and IV antibiotics. In the survey we conducted, patients have recorded between 1 and 12 exacerbations a year, highlighting the great variability in how the disease affects this population. Patients described the regular use of antibiotics and

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noted many instances where they would need to adjust how their exacerbations were treated when they no longer responded to some treatments or when they experienced severe side effects.

Reducing overall systemic antibiotic use ranked as the third most important outcome in our first patient survey. Patients expressed a desire to have an inhaled option that can lower the overall amount of systemic antibiotics and deliver more targeted benefits. They understand that there is a risk of developing resistance to any antimicrobial treatment, but they also faced the urgency of preventing even one more exacerbation, which could sadly turn out to be their last.

We understand that the long-term safety profile of potential non-CF bronchiectasis is an important consideration. However, given the serious unmet need in this population, the patients existing use of systemic antibiotics and the danger that is posed to patients by participating in a placebo controlled trial for long periods of time should also be considered as an important factor.

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We applaud the FDA for your commitment to increasing the use of patient perspectives in your decision-making and urge you to strongly consider the severity of disease burden and current unmet need as conveyed by the community as the agency determines how best to move forward.

We remain committed to working with the FDA as you seek to address the immense unmet medical need in the non-CF bronchiectasis population and look forward to discussing how to better identify and integrate patient perspectives in the regulatory review process. Thank you for your time and consideration.

DR. SMITH: Thank you.

SESSION 2: NON-CF BRONCHIECTASIS:
CURRENT LANDSCAPE, CHALLENGES AND CASE STUDY

DR. O'Donnell: So Dr. Smith from the FDA is going to address the historical perspective of product development in non-CF bronchiectasis.

NON-CYSTIC FIBROSIS BRONCHIECTASIS: HISTORICAL PERSPECTIVE OF PRODUCT DEVELOPMENT

DR. SMITH: Thank you. You'll notice that this talk is only 5 minutes in length and that's

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because of the unfortunate situation that we don't have anything approved for the treatment of non-CF bronchiectasis.

Studies of -- previous studies of inhaled antibacterial drugs, which I'll be showing on the next couple of slides, have yielded mixed results, and there are a lot of uncertainties regarding the duration of treatment and the frequency of administration and appropriate endpoints for this use. There are no animal -- relevant animal models of non-CF bronchiectasis to explore dosing regimens, duration of therapy or to provide supportive information.

You'll notice this is just a sampling of some of the trials of inhaled antibacterials for non-CF bronchiectasis. And what you'll notice here is there are a variety of treatment regimens that have been studied, there are different endpoints -- primary endpoints that have been looked at, and there's -- the studies by and large are small studies and there are lot of inconsistencies in the treatment effects that have been observed.

In the studies of tobramycin, for instance,

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you know, there was some decrease in pseudomonas sputum, in the sputum at 4 weeks and something that was termed improved medical condition, but there were no differences in FEV1 percent predicted and more adverse events with tobramycin. And the same kind of pattern holds true for some of these other antibacterials that have been studied.

We had a workshop 6 years ago that addressed issues in the design of clinical trials for non-CF bronchiectasis and there was a lot of discussion about the patient populations, and again, as we just heard, you know, the heterogeneity of the non-CF bronchiectasis patient population was discussed in terms of the etiologies, in terms of the patient presentations and the clinical course of patients.

There was also discussion about whether the objectives of trials and therapies should be to treat exacerbations as opposed to prevention of exacerbations. There were presentations about disease-specific patient-reported outcome measure, The Quality of Life-Bronchiectasis measure; discussion about pulmonary exacerbations and how to define them and what

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the best endpoint in terms of evaluating exacerbations would be, and this would include time to exacerbation, frequency of exacerbations or whether there were other analyses that might be more appropriate.

The issue of safety has to do with trying to sort out with adverse events whether they are due to a problem with the drug tolerability of inhaled therapy versus progression of disease. And often these adverse events confound the analysis of the primary endpoint in trials that are directed towards preventing exacerbations.

We've had two Advisory Committee Meetings in the past year. These were to discuss the ciprofloxacin dry powder for inhalation and ciprofloxacin dispersion for inhalation. These programs were similar in that they were 48-week phase 3 trials of intermittent cycles of inhaled ciprofloxacin and placebo. The primary endpoint for both programs was time to first exacerbation. The secondary endpoints included frequency of exacerbation, patient-reported outcome measures and FEV1 percent predicted.

And what you see here -- and those of you who

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attended the committee heard this, committee meetings -- for the ciprofloxacin dry powder for inhalation, the primary endpoint was not met for 3 of the 4 test arms. There was a lack of replication of findings across trials and a lack of consistency of findings across endpoints within the same trial. For the ciprofloxacin dispersion for inhalation, there was one failed trial and a lack of clear explanation for discordant findings between the two trials.

The issues that were discussed at the Advisory Committee Meetings included the clinical relevance of the observed treatment effects when the risks such as adverse reactions and the development of resistance were considered. There was a discussion about the durability of the efficacy and safety findings over time, which included the development of resistance. And there were concerns that the long-term use of inhaled ciprofloxacin could limit the utility of systemic fluoroquinolones for the treatment of severe exacerbations or pneumonia in non-CF bronchiectasis patients.

Some of the comments that we received from the

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Advisory Committee included that the time to first exacerbation may not be the best primary endpoint and that frequency of exacerbations was clinically more meaningful. They recommended considering additional measures such as the severity of exacerbations, hospitalizations, the need for intravenous therapy, total days of antimicrobial therapy, changes in pulmonary functions and quality of life measures.

Regarding the duration of trials, you know, the difficulty with the frequency of exacerbation endpoint is that a 1-year trial may not be of sufficient duration to detect treatment differences.

There were recommendations to try to reduce the heterogeneity of the patient population by attempting to standardize adjunctive therapies or to require a minimum number of exacerbations within, say, the previous year for enrollment.

And the committee did note that antimicrobial resistance was a major concern that might limit -- you know, in terms of the durability of the treatment effect and limit the utility of the parent drug for more severe infections.

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So what we'll do for the rest of the afternoon, we're going to have Dr. Tino discuss the state-of-the-art in non-CF bronchiectasis care. We have a presentation from Jasan Zimmerman, who has participated in the last couple of Advisory Committee Meetings from the patient perspective. And then we will have a case study and discussion focusing on patient selection and endpoint considerations. Thank you.

DR. O'Donnell: Dr. Tino -- Greg Tino from the University of Pennsylvania will give us an update on the care of patients with bronchiectasis.

CARE OF THE BRONCHIECTASIS PATIENT: CURRENT STATE

DR. TINO: Thanks, Anne. And I'd like to -- before I start, I like to thank the FDA for bringing this workshop together and for asking me to participate.

So my job over the next 30 minutes or so is to give you an overview of the treatment approaches in 2018 for our patients with bronchiectasis not related to cystic fibrosis.

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Perfect, thank you. These are my disclosures. And by way of a brief introduction, bronchiectasis is characterized pathologically by airway inflammation and permanent bronchial dilatation, and clinically by profound respiratory symptoms, including cough and chronic sputum production.

And as been mentioned before, it's a heterogeneous entity with multiple etiologies. And there is data now both from the United States as well as from Europe that its prevalence is increasing year to year, especially in the older populations. And importantly, the clinical course is punctuated by exacerbations, which, as generally defined, are really acute respiratory tract infections that require systemic or other therapies for resolution.

And importantly, this is a syndrome that's associated with notable impairment of quality of life as well as significant mortality and morbidity.

And this is a slide that illustrates the adverse impact of bronchiectasis on overall quality of life. So this slide looks at the St. George's Respiratory Questionnaire, which is a longstanding and

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oft-used quality of life measurement for lung diseases. And if you compare bronchiectasis to other more common and more devastating or previously thought to be more devastating lung diseases like idiopathic pulmonary fibrosis, advanced COPD, cystic fibrosis and server asthma, you'll see that the impact of this disease on the quality of life is akin to what we see in those other conditions. And importantly, we'll come back to this.

If you look at the left-hand bar of the slide, in those patients who have bronchiectasis who also have concurrent chronic pseudomonas infections, and that accounts for about 30 percent of our patients, that impairment of quality of life is even more profound.

Now, as a clinician, it's important for me to establish the goals of therapy for my patients, and this is best done obviously in conjunction and in discussion with our patients. So potential goals of therapy in bronchiectasis include to control symptoms, particularly cough and sputum characteristics; to maintain lung function; to improve quality of life; to reduce exacerbations -- and this is where we spend lots

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of our time in the clinics, discussing the options to do that -- reduce mortality; and finally, to reduce the cost of care.

Now, while it's easy to come up with a list of treatments or at least a list of goals of treatment, what becomes more challenging in this disease is to really establish these particular endpoints as endpoints for clinical trial and the assessing of the efficacy of treatment modalities on some of these goals and some of these endpoints.

For example, in terms of lung function, it's very clear that FEV1 is an important number. The lower the FEV1 has been associated with adverse natural history and advanced morbidity and mortality and it clearly is important one assesses the safety of delivery of inhaled drugs. But in general, the FEV1 does not appear to improve with therapy. So that -- in general our aim is to stabilize lung function as possible over time.

Quality of life, we spent some time talking about. Unfortunately, there is no fully validated method of assessment and we clearly need additional

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help in this area.

Exacerbations, which have been the focus of most of our clinical trials, as I'll describe, the definition has been difficult to establish. I think we've made some progress and I'll present that to you, but we've got some other work to do to hone down on the definition and then really assess what are those endpoints that we need to look at, time to exacerbation versus frequency -- and I'll tell you my opinion later on. And finally, mortality obviously is difficult to study in relatively short-term trials.

So in terms of pulmonary exacerbations, again this has been a bedeviling topic for those of us who do work both clinically and in the research arena for bronchiectasis.

What I'd like to show you is a recent publication from the European Respiratory Journal, which was really the coming together of international experts to come up with a consensus definition using the Delphi approach to define a pulmonary exacerbation.

So what we came up with is, and which was published in the European Respiratory Journal in 2017,

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is that the definition of a bronchiectasis pulmonary exacerbation for clinical trials is a person with bronchiectasis who exhibits a deterioration in three or more of the following key symptoms for at least 48 hours: cough, sputum volume and/or consistency, sputum purulence, breathlessness and/or exercise intolerance, systemic symptoms like fatigue and/or malaise, and the last is haemoptysis. And importantly, an important part of this definition is that a clinician determines that a change in bronchiectasis treatment is required.

So that summarized the current state of therapy of bronchiectasis. Unfortunately, as has been mentioned, there are no approved therapies, and available clinical guidelines regarding management options or really based on low to very low quality of evidence. And the clinical trials for many of the pillars of treatment that I will talk to you about are lacking today.

I always like to start with a case presentation, a brief case presentation. This is a patient whose case I've presented in many different forums because I think he illustrates and his course

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illustrates some of the important challenges that our patients face.

So this is a 77-year-old gentleman who was actually diagnosed with bronchiectasis at age 12 after developing pneumonia as a young child. This is what his scan looks like, and as you can see, very advanced cystic bronchiectasis involving his entire left lung as well as the right middle lobe.

Interestingly, he did well for many years and he was managed with regimens that included rotating systematic antibiotics, which was quite commonly used in previously years, and as well as airway clearance.

But the last several years have really not been kind. And I've outlined here and underlined some of the major changes that have impacted him and that characterize many of our patients. He now has a quinolone-resistant chronic pseudomonas aeruginosa infection. He has frequent exacerbations, three to four per year that often require hospitalization and intravenous antibiotics. He produces large volumes of purulent sputum, up to 40 milliliters per day, and he clearly perceives that his quality of life is

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declining.

Again, these are the challenges: recurrent exacerbations, chronic gram-negative infection, impairment of quality of life and voluminous sputum production.

So when I approached the treatment of bronchiectasis, what I used as a conceptual framework is the viscous cycle framework that was proposed back in the late '80s by Dr. Peter Cole to really simplify the approach of the pathogenesis of bronchiectasis.

So the viscous circle or the viscous cycle hypothesis starts with an inciting event, usually an infection in the susceptible person, which leads to neutrophilic inflammation, protease activation and the development of airway destruction, i.e., bronchiectasis, which leads then to abnormal mucus clearance, which sets up the opportunity for chronic -- bacterial colonization and chronic infection. And this viscous cycle of infection and inflammation propagates airway injury.

So when I approach the options of therapy, I look at how can we interrupt different parts of the

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cycle. So the mainstay of the treatment of bronchiectasis is antimicrobial therapy, both systemic to treat exacerbations -- and we'll talk about inhaled antibiotics -- in a chronic suppressive fashion. Anti-inflammatory or immunomodulatory therapy can be employed. We'll talk about macrolides and a little bit about systemic inhaled corticosteroid therapy.

Airway clearance to deal with the sequel (ph) of abnormal mucus clearance is very commonly and should be very commonly applied in these patients. And then for a smaller number of patients, surgery can be applied in certain circumstances, and I'll describe that to you in a little bit.

And then finally, when an underlying condition is identified that has caused the bronchiectasis, the treatment of that underlying condition obviously when appropriate is a very important part of the therapeutic approach to these patients.

Now, the Bronchiectasis Research Registry of the United States has been instructive in a number of ways. And this is our first publication describing our first look at our registry. And this was a report of

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our first 1,826 patients with a physician-established diagnosis of bronchiectasis who were enrolled between the years of 2008 and 2014.

And what I've pulled out from here is really to illustrate the variability with which some of the therapeutic options are applied across a group of centers with expertise in this disease.

So airway clearance is applied in only half of our patients. Antimicrobial drugs are used in about 40 percent of the time just to treat exacerbations. About 40 percent of the time antibiotics are used in suppressive fashion, 10 percent in aerosol delivery and 7 percent with rotating oral regimens.

And then you'll see here inhaled bronchodilators, inhaled corticosteroids and systemic corticosteroids are applied in a fairly robust group of patients in the absence of any data suggesting efficacy. So again, we've got treatment options out there, but they are applied variably across the landscape in this country.

So let's focus on some of the specific measures, and the first is airway clearance. An airway

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clearance refers to a group of techniques that are designed to enhance mucociliary clearance. As an expert in this field, I think that we will all agree that these measures are considered mainstays of management of patients with bronchiectasis. And yet there's very little data establishing the efficacy of airway clearance in general or some of the modalities specifically.

Now, there are a number of modalities that are in use, both mechanical and pharmacologic. The vibratory PEP devices -- and you can see several of the devices that are in use clinically here. And it turns out that PEP valve use is most common in our U.S. Bronchiectasis Registry. There are also a number of what I call higher tech options, including high-frequency chest wall oscillators that are in use across the United States.

With regard to pharmacologic agents, there has been a focus on hyperosmolar agents, number one, inhaled mannitol. As you know, inhaled mannitol is bronchoprovocational agent, but in some early studies it was found to have a profoundly important impact on

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sputum rheology. A phase 3 trial was convened and accomplished. Unfortunately, there was no significant reduction in exacerbation rates, which was the primary endpoint. And this is not available for clinical use.

Hypertonic saline, which is now an established modality in cystic fibrosis. Unfortunately, has not been studied in large-scale clinical trials. There's one small trial that suggested an improvement in sputum rheology, an improvement in St. George's Respiratory Questionnaire and a decrement in annual antibiotic usage. But the quality and the size of this trial really, I think prevents clear-cut evidence-based application of this in a confident fashion.

With regard to other pharmacologic agents, I just wanted to mention the fact that bronchodilators, as I mentioned to you, are commonly used, but there is really no long-term randomized controlled trial data to suggest efficacy as an airway clearance drug. And the use of bronchodilators I think should be restricted to those conditions where bronchodilator therapy is indicated, including COPD and underlying asthma.

And I put up mucolytics here and specifically

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referring to rh DNase to really remind you that the lessons learned for cystic fibrosis cannot always be applied across the board to non-CF bronchiectasis. And this is a case in point. Rh DNase was studied -- very well studied in cystic fibrosis and is now a part of the treatment armamentarium. But in a large-scale clinical trial that Anne O'Donnel did a number of years ago, rh DNase was not only not effective in non-CF bronchiectasis, but potentially deleterious. And again, we've got to keep that in mind that works in cystic fibrosis may not necessarily work in non-cystic fibrosis-related bronchiectasis.

So what's the current state of airway clearance? The recommendations are that those patients that are targeted should be symptomatic patients with chronic cough and sputum production, those who have difficulty expectorating sputum, those who have impairment of quality of life and frequent acute exacerbations.

You see that this was discussed in the recently published European Respiratory Society Guidelines. In this group, airway clearance received a

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weak recommendation based on low level of evidence. In general, and practical terms what we typically recommend is a modality that will maximize patient adherence and typically that's one of the PEP valves and on occasion hypertonic saline.

I won't spend a lot of time discussing systemic antimicrobial therapy for exacerbations. I just want to make a couple of points. One is that sputum analysis is critical. This is something we spend a lot of time teaching our trainees and collaborating with our community-based physicians.

And the bacteriology of bronchiectasis can be summarized. Here, you'll see that haemophilus influenza and pseudomonas account for the two most commonly isolated bugs in these patients, about a third of the time. And you can see the rest of the distribution there.

But I think you also see on the slide that in a fairly sizeable group of patients about 20 percent to 25 percent of the time a dominant pathogen is not identified and it underscores the importance of empiric antibiotic choice in these patients. And more recently

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our experience from the Bronchiectasis Registry, again, pseudomonas aeruginosa accounted for 33 percent of the isolates and staph aureus about 11 percent.

So the general principles I wanted to leave you with is that there are some very challenging pathogens, including pseudomonas and staph, particularly MRSA, that in general the empiric antibiotic choice should be directed at those common pathogens with adjustment and narrowing of the antibiotic choice of a specific pathogen as isolated.

In terms of the optimal duration, the current recommendations based on again ERS' guideline is a 14-day course. This is a conditional recommendation again based on very low level of evidence. But in general, a longer course is often utilized, 21 to 28 days, as dictated by the clinical response.

Now, turning to inhaled therapy, inhaled antibiotic therapy, obviously we've had a lot of discussions today about its use -- or the use of these drugs in cystic fibrosis. In non-CF bronchiectasis, there has been a lot of focus on this, primarily in use as a chronic suppressive approach to chronic infection

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in patients with bronchiectasis.

The focus and the targets of inhaled antibiotics have been patients who have chronic infection with gram-negative organisms, particularly pseudomonas, and those who have frequent exacerbations with the goal of reducing those exacerbations.

And frankly, as I look at the data, I think that the targeting and the choosing of those targets I think is well-founded based on some of the things I'm going to show you in a second.

So first is bacterial load. It is very clear that chronic infection is associated with high bacterial load and these high bacterial load, high CFUs lead to risk of future exacerbations, increased risk of hospitalization for exacerbations and higher and more profound elevations of markers of lung inflammation. This was done in a very nice study by Dr. Chalmers back in 2012. And we know that antibiotics, both systemic and inhaled, can have a profound impact on markers of lung inflammation, in reducing colony forming units, and we hope, in reducing exacerbations and hospitalizations among other endpoints.

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Now, we spent a couple of minutes talking about the fact that this is a heterogeneous disease with many different etiologies, but one of the developments of the last several years is really a face shift not so much away from looking at specific etiologies, but really trying to establish phenotypes. And a phenotype is really a group of clinical characteristics that really define a clinical condition.

And in a very elegant paper that was recently published in the Blue Journal, Dr. Chalmers and his collaborators really defined and identified a frequent exacerbator phenotype. This was based on a study of 2,500 patients from 10 sites in Europe and Israel. In this cohort, about 40 percent of the patients only had zero or one exacerbation over a period of follow-up, and 37 percent had three or more on a yearly basis. And it turns out that prior and frequent exacerbations were the strongest predictors of future exacerbations.

Other independent predictors of this frequent exacerbated phenotype, including those who had chronic infection with haemophilus and with pseudomonas, those

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who had severe diminutions in FEV1, those with multifocal bronchiectasis and radiographically severe bronchiectasis and those who had co-existing COPD.

Importantly, frequent exacerbators also had worse quality of life, high disease severity as assessed by the bronchiectasis severity index and increased mortality across the board.

I've described to you that gram-negative infections have been the focus of a lot of the work with the use of inhaled antibiotics, but specifically pseudomonas aeruginosa.

And this is again data published from Europe that looked at the impact of chronic pseudomonas infection on hospitalization and mortality over a period of several years. And if you look on the left, you can see that people who are chronically infected with pseudomonas have a sevenfold higher risk of hospitalization over the period of follow-up as compared to other pathogens or in comparison to those patients who don't have a dominant pathogen identified. And the same holds true for mortality, with a threefold higher rate of mortality in patients with chronic

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pseudomonas infections relative to others.

But if you look at the second bar in each of the graphs, other gram-negative infections, stenotrophomonas, chromobacterium (ph), et cetera, those are bad actors as well, pseudomonas being the baddest actor. But those other gram-negative rods are something that we pay a lot of attention to.

And then finally, obviously as we've talked about, inhaled antibiotics have been the standard of care in CF patients and tobramycin and aztreonam have been in clinical use. And the hope had been that we can establish the efficacy of inhaled antibiotics in non-CF bronchiectasis as well.

Obviously, there are many attractive features of inhaled antibiotics. They definitely develop high concentration in the airway, reduced systemic absorption is pretty commonly seen, and this leads, we think, to reduced systemic toxicity. And when you're dealing with a group of patients in an older age group, this is a particularly attractive group of pros. There are some cons, obviously, airway side effects, which are well described. And again, we've had the start of

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a robust discussion on resistance and I'm sure this will continue this afternoon.

Now, inhaled antibiotics are very commonly used or commonly used as we saw in the U.S. Bronchiectasis Research Registry. But if you look at a deeper dive at our registry, if you look at patients who have frequent exacerbations, again about 30 percent of the patients in the registry have been treated with inhaled antibiotics. And the rest of the data underscores the fact that patients with frequent exacerbations continue to have exacerbations and are predictive of future exacerbations and have a higher rate of hospitalization, as indicated on the slide.

Now, there a number of published guidelines about inhaled antibiotics from Spain, from the U.K. and from New Zealand and Australia. I am not going to go through these in detail. But the common theme is that inhaled antibiotics should be considered for patients who have frequent exacerbations -- and we can discuss how we describe the severity or the number of frequency of exacerbations -- and those who have got chronic pseudomonas infections. That's a recurrent theme in

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the application of inhaled antibiotics.

Now, the good news is over the last several years we've had a number of clinical trials that have been accomplished and published in the literature, and I think Dr. Smith has already touched on briefly a couple of them and I would like to touch on the ones that are highlighted here.

Now, there have been several trials of inhaled tobramycin. You can see the references on my slide. And I will just by the way of summary just say that what has been shown is a profound microbiologic impact on pseudomonas aeruginosa with profound decrements in colony forming units while patients were on inhaled drug, without the obvious emergence of clinically meaningful resistant organisms. There has been improvement in clinical symptoms and quality of life that have been suggested.

But unfortunately for a number of reasons the efficacy as either to maintenance therapy, chronic suppressive therapy or in one study where it was looked at for the treatment of acute exacerbation, this has not yet been established and there are clearly adverse

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effects -- what we call airway symptoms, characterized by cough, dyspnea, bronchospasm -- have been well described. In many cases, these adverse airway effects are nuisances and in some patients, it results in discontinuation of a drug.

More recently, the experience with inhaled colistin -- this was a study published several years ago -- the experience of 144 patients with chronic pseudomonas infection who were randomized to get inhaled colistin versus placebo on a daily basis for up to 6 months. These folks were enrolled within 21 days of an acute exacerbation. The primary endpoint in this trial was time to exacerbation. The secondary endpoint was time to exacerbation based on adherence, bacterial density, St. George's Respiratory Questionnaire, as well as other safety parameters.

The primary endpoint in this trial was not met in the intention-to-treat group, but there were some signals there: there was a significant reduction in pseudomonas colony forming units at 4 and 12 weeks, there was an improvement in the St. George's Respiratory Questionnaire of about ten and a half

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units, which is thought to be clinically significant; and the drug was well tolerated.

If you look at a subset of patients, in adhering patients, that is who were found to be able to take more than 80 percent of their doses, the median time to exacerbation was increased 168 days in the colistin group versus 103 days in the placebo group. And you can see the 'p' value there. The exacerbation rate was 50 percent in the colistin group and 72 percent in the placebo group. And as a result of this trial, there's now a convened international, multinational trial of inhaled colistin in non-CF bronchiectasis which is ongoing.

The RESPIRE 1 and 2 trial and the ORBIT 1 and 2 trials are very well known to this committee and to this group. These were recently presented. The data was recently discussed at two Advisory Committee Meetings, two separate Advisory Meetings.

Just to get us on the same page, the RESPIRE 1 and 2 trials were phase 3 double-blinded trials of twice daily ciprofloxacin DPI either on a 14 or 28 day on or off regimen for 1 year -- 48 weeks. Patients

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enrolled had greater than two exacerbations in the preceding 12 months, which was stringently defined; seven pre-specified pathogens, including pseudomonas. You can see the FEV1 parameters there. The primary endpoints were time to first exacerbation and number of exacerbation events.

And the results with regard to the primary endpoints -- and these were published more recently by Dr. Aksamit and his colleagues in ERJ -- you can see that in RESPIRE 1 there was a significant increase in median time to first exacerbation and a 39 percent reduction in frequency exacerbations. But this was not replicated with regard to the primary endpoint in Respire 2.

Then ORBIT 3 and 4, again these were phase 3 identical trials using once daily liposomal ciprofloxacin, 48 weeks on, with six cycles of 28 days on and off and then a 28 open-label extension. This was specifically targeting chronic pseudomonas infection with at least two exacerbations in the preceding 12 months. Exacerbations and severity was defined in the protocol. And you can see the primary

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endpoint was time to first exacerbation. The secondary endpoint was frequency over a 48-week period.

And again, these data have been presented in abstract form and in the Advisory Committee. And you can see that in Orbit 4, there was a significant increase in median time to first exacerbation and a reduction in frequency of exacerbations that were seen in the pool data as well. But again, could not be replicated in ORBIT 3. What was demonstrated was pretty consistent, that there was a decrement in sputum density of pseudomonas patients who were on the drug.

So what is the current state of affairs in inhaled antibiotics? Well, there's a clear microbiologic effect, but unfortunately the clinical efficacy based on traditionally used endpoints has not been proven conclusively. There are none that have currently received approval by regulatory agencies. And we'll talk about this. But the emergence of clinically meaningful resistant pathogen has not been observed thus far in these clinical trials.

So where do we stand in terms of target populations? Typically, it's those who have chronic

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gram-negative infection, particularly pseudomonas; those who have frequent exacerbations, 2 to 3 year; and who have other therapeutic options optimized, but lots of unanswered questions, including daily versus on or off regimens; and the relationship to chronic macrolides again has not been established.

I'm going to turn to chronic macrolide therapy. This is really a very interesting development. The macrolides have myriad of anti-inflammatory and immunomodulatory properties, which really give it scientific plausibility when implied to bronchiectasis. And you can see the list of those anti-inflammatory, immunomodulatory properties. And certainly, there is precedence for use in other airways disease like CF, diffuse panbronchiolitis, post-transplant obliterative bronchiolitis as well as COPD.

Now, there have been three large -- relatively large clinical trials that have been performed, and published and this slide summarizes the three trials, EMBRACE, BAT and the BLESS trials. You can see the number of patients enrolled in each of the trial. There were clearly differences in enrollment criteria.

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One study focused on those who had at least one exacerbation in the past year and one on more than three exacerbations. Two of the studies uses azithromycin; one used erythromycin. And you can see the endpoints that were looked at in the different trials.

But suffice it to say that all three trials, all three studies which were published in high-quality journals reported significant decrement in exacerbations in patients with non-CF bronchiectasis.

Now, of course there are concerns about the longer use of macrolides, concerns about the development of bacterial resistance for commensal organisms in the respiratory tract, a concern about the potential for macrolide resistance in patients who have concurrent nontuberculous mycobacterial infection. There's well-described cardiac risk, specifically in those who have cardiac comorbidities, and obviously other adverse effects, including GI tract symptoms and ototoxicity in the long term.

So the current state of affairs and where we target macrolides is patients who have frequent

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exacerbations, who will have no underlying cardiac disease and normal electrocardiograms. In general, the recommendations are that we avoid the use of macrolides in patients with known or strongly suspected anti-M infection. This becomes particularly problematic if you practice in Southeastern Pennsylvania, where we see lots of nontuberculous mycobacterial infections. And the duration of therapy has not been established beyond what we've seen in clinical trials.

I'm going to skip this slide for the sake of time. Now, I just like to spend some time telling you what's not recommended. One of those is inhaled corticosteroid therapy. One would think that this is an inflammatory airways disease so there may be some role for inhaled corticosteroids. Well, there is really no convincing data to support the routine use of inhaled corticosteroids in patients with bronchiectasis and there is some recent publication suggesting a possible increased risk of nontuberculous mycobacterial infection in patients with bronchiectasis treated with inhaled corticosteroids.

I alluded to the fact that my patient had

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received rotating systemic antibiotics. And in general, as of now there is no evidence-based data to support the use of systemic non-macrolide suppressive or maintenance therapy. And again, in terms of chronic systemic corticosteroids, there is no mandate to use those on routine basis, except to supply it for specific populations, for example, for those with allergic bronchopulmonary aspergillosis.

I mentioned surgery as an option. Again, this is really applied in the minority of patients and the current state of affairs is that this is an option for patients who have got localized bronchiectasis who have frequent exacerbations despite medical therapy. It has been used successfully as adjunct to medical therapy for those with anti-M infection and occasionally is necessary in patients with refractory and massive hemoptysis.

Now, there are no trials comparing medical therapy to surgical therapy in these patients, but those surgical trails that have been published have shown that in fact that surgery in patients with bronchiectasis in that target population can be

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performed with acceptable morbidity and low mortality.
Obviously, other supportive measures, specific therapy when appropriate, systemic corticosteroid therapy for allergic bronchopulmonary aspergillosis, immunoglobulin replacement therapy for immunodeficiency, et cetera, are a very, very important part of what we do.
We will use some short-course systemic steroids for some exacerbations that are associated with significant bronchospasm, aerobic exercise and pulmonary rehabilitation, supplemental oxygen in those who require it and lung transplant can be performed successfully. So the treatment of bronchiectasis again includes some of the stuff we talked about, but supportive measures are of particular importance.
I'm going to skip this as well. So at the risk of sounding self-serving, this is an editorial that I wrote in conjunction to Dr. Chalmers' paper about frequent exacerbations and this I think summarizes the state of affairs in bronchiectasis. And the sobering reality is that our patients with bronchiectasis suffer significant mortality and

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morbidity and yet can be offered few proven effective therapies. And ultimately, we need better characterization of our patients; more high-quality clinical trials to further define this entity; and most crucially, better therapies, antimicrobial or otherwise; and the process of adoption of this orphan disease by clinicians and researchers needs to be accelerated.
But where there are challenges, there are opportunities and we as a community of physicians and researchers and patients have the opportunity to better characterize the epidemiology and natural history of this disease, to strengthen and support for and expand patient registries. We've seen the results from the European Respiratory Society and from the European Bronchiectasis Registry, EMBARC, as well as our United States bronchiectasis registry. We're making major inroads in establishing some of the epidemiologic and natural history characteristic.
Again, we need to rethink endpoints for clinical trials and address some of the regulatory challenges -- and I look forward to our discussion in

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the next few minutes -- and importantly, to identify new targets for treatment.
So I thank you very much for your attention. Again, look forward to our discussion and the panel discussion.
DR. O'DONNEL: Okay, thanks, Greg, for that talk. And next is -- we want to hear the patient perspective. The patient speaker is Jasan Zimmerman, who is going to present the perspective of a patient with bronchiectasis.
PATIENT SPEAKER/PATIENT PERSPECTIVE
MR. ZIMMERMAN: Thank you to the FDA for inviting me and thank you to Dr. Tino for that great overview. Thank you to everyone who is participating today and thank you to the audience for watching, those who are in the room and those who are online, especially my wife and my parents.
I want to preface this by saying I'm only one person, and as we've learned today, this disease is so varied and variable that you're getting my perspective and hopefully some perspectives of other things that I've learned, but it's ultimately only my perspective.

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I really appreciated Mary's sports and balls analogy. I thought that was great. Some days I'm a baseball, some days I may be a tennis ball, some days I may be a shot put, and it just depends on how I feel that day and it's really indicative of the variability of the disease.
I've had lung issues my whole life. When I was really young, I was diagnosed with asthma, constantly wheezing, having asthma attacks. In 1984, when I was 8 years old, I had a partial lower left lobectomy. That part of the lung was filled with abscesses. No bacteria or viruses were cultured, but it was some kind of an infection.
So I dealt with that growing up. And then, in 2011, I had pneumonia on the right side -- in the right lung. I will go into that a little bit more, but that's when my bronchiectasis was diagnosed. I was 35-years-old. I have a pretty big spot of bronchiectasis on the right side and I have areas of consolidation throughout the rest of the -- both of my lungs.
In 2013, I was diagnosed with allergic bronchopulmonary aspergillosis. Maybe that contributed

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to the bronchiectasis, who knows? I think it's again indicative of the different paths to the disease.

My concerns are varied and many. I always get nervous when I'm around sick people. Lots of people come to work sick and I hear them coughing and hacking and that makes me nervous to get sick myself. Travelling is always difficult. You're trapped in a plane -- yesterday my flight from SFO was about 5 hours, trapped in a plane with who knows, what kind of sick people or not.

I'm also concerned about my lung function and exacerbations: Am I going to be able to continue my life as I live it now without making many lifestyle changes? Can I still ride my bike to work? Can I still exercise?

And like I mentioned, pneumonia is a big concern for me. I have a long history of pneumonia as well. Growing up as a kid, I had it several times. And then when I went to college, I began this period of getting pneumonia when I was very stressed and highly anxious, lack of sleep, lack of exercise, probably poor eating as well.

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So I got -- the first time I was diagnosed with pneumonia right before spring break of my freshman year in college and then during spring break of my first year at grad school. And then I took some time off and went back to school. And during my second grad school time, I was diagnosed again with pneumonia in the summer between the 2 years.

That was the worst one. I was in the hospital for 6 days. I was off work on short-term disability for about 3 months, on oral antibiotics for 2 months. And that really underscored for me the importance of keeping my lungs healthy and also showed me how terrible pneumonia was and how I don't want to have that again. So that's always in the back of my mind, that fear.

I'm also concerned about antibiotic resistance and side effects. I've been on and off antibiotics for my whole life. And as we heard from Amy about her stepmom, those are some systemic issues that can occur. What's going to happen to me as I grow up or as I get older? Will I have systemic effects? Am I at a higher risk for resistance and virulence? I've had

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pseudomonas infections in my sinuses, is that something I should worry about with my lungs?

So the physical stuff is difficult to deal with, but I think by far the most difficult for me is the psychological issues and worry and anxiety. I don't want to get sick and I worry about not wanting to get sick. And I hear from other bronchiectasis patients. It's great especially in this forum and at the last couple of advisory panels. It's really awesome to hear their stories and hear how they're trying to change what's going on. It's also very sobering for me because I can see what the disease progression is like and that makes me worry a little bit more as well.

I spoke with my pulmonologist last week to kind of get a better sense and make sure that I had all my dates right for my disease progression. So a big thanks to Dr. Judy Wong at the Palo Alto Medical Foundation. I asked her what kind of bronchiectasis patients she had and she said she has lot of bronchiectasis patients, and they're also concerned with the number of exacerbations and long-term

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antibiotic use, as we've heard a lot of that today.

Many of her patients -- I asked her what some of the really big issues were. And she said many of her patients just let their flareups of bronchitis or some other lung infection go and they don't seek immediate treatment. And then she sees more bronchiectasis, as we saw with Dr. Tino's vicious cycle.

So that just underscores for me that I really need to make sure that once I start feeling bad, I go see her and try to figure out how to take care of it.

Dr. Wong also mentioned that CF patients are used to being patients -- like Chip mentioned to me that he was diagnosed with CF at age 3 and so he's been a patient for his whole life and I don't think all non-CF bronchiectasis patients are like that, especially with the late onset. So there has to be a lot of education for these patients so that people know the importance of immediate treatment and not letting stuff go.

CF bronchiectasis just has the one path and non-CF bronchiectasis can come from various different

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diseases or other things that we've heard about today. So it's so much more difficult to treat, as we've been hearing all day.

I was lucky enough to participate on the last two Advisory Committee panels for Bayer and for Aradigm and I actually advocated for longer clinical trials to address the antibiotic resistance.

I had a conversation with Amy Leitman, who we heard from earlier today from NTM Info and Research, and Jamie Sullivan from the COPD Foundation, and they really changed my mind. And hearing everything today this morning and this afternoon, that really reinforced that my mind has been changed.

I hadn't taken into account the people that had been given placebos -- and Dr. Nichols touched on this, Chip touched on this, so did Cara and Amy. Can they survive being off of their regular treatment for that long? Is that fair to them? Is it ethical? They'll still have the standard of care available for a flareup or whatever, but is that really a good idea?

So that made me change my mind and made me think -- like Dr. Tino mentioned, we need to rethink

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the endpoints for clinical trials so that they're much more relevant for patients. Can we use maybe some CF endpoints or translate them into non-CF bronchiectasis?

Cara mentioned the survey of nearly 300 bronchiectasis patients and that lung function and the number of exacerbations each year ranked as the top 2 concerns. And those are very similar to my concerns as well.

So it's obvious to me the quality of life of patients must be taken into account when we're designing these trials. Do people feel better when they're taking the drug and do they feel worse when they're not taking the drug? Are the existing quality of life surveys adequate for capturing how people feel? Are they adequate enough to be used as an endpoint? Well, let's figure this out, I think like Mary mentioned as well.

I like to also leave you with some calls to action. It's obvious that we need more non-CF bronchiectasis research and clinical trials.

And I'm struck by the number of disclosures that were in the agenda. All of the medical

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professionals here have "consultant" for this drug company, "on the advisory board" for this drug company. Chip and I don't have those disclosures. Why aren't patients involved in those kinds of things? Why aren't patients on advisory boards? Why aren't patients consultants to help design these drug trials?

There's lots of discussion today about trial design and the drug development process and we haven't heard anything about patient input in either of those. We need more diverse patients to be involved in clinical trial design. Diverse meaning ages, socioeconomic status, races, locations, a balance between men and women. And we need that with the industry partners as well as the FDA.

It would be great to have more validated patient-reported outcomes and quality of life surveys to be developed by the FDA. They can do that in conjunction with patient representatives and with community-based organizations.

The patients are the experts. They know when they feel good on a drug and they know when they don't feel good when they're either on a drug or not on a

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drug, and that has to be taken into account in these trials. The patient-reported outcomes should be included in every trial so that we can determine the effectiveness of the trial.

It will be great to have more of the pulmonary division of the FDA involved. I know we have one person here. And I'd like for them to be involved in the clinical trial design as well and not just the antimicrobial group.

We talked about pharmacovigilance earlier. That will be great to have that to take into account antibiotic resistance and virulence after the drug is approved and other side effects, not just for antibiotic resistance. But people could be on these drugs for decades. So we need to follow them and make sure that everything is safe.

I want to thank Bayer and Aradigm for participating in these conversations and for trying to get these drugs approved. Please continue to develop these inhaled treatments so that we can get these drugs approved with patient input of course and get them into the hands of the people who need the most, and like

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Chip said, make sure there are choices for patients like me. Thank you very much.

DR. O'DONNELL: Thank you. Thank you, Jasan, very much. Got a lot to think about. So we're going to take a break till 2:30. So we'll reconvene at 2:30. Thank you.

BREAK

CASE STUDY ON DEVELOPING AN INHALATIONAL THERAPY FOR NON-CYSTIC FIBROSIS BRONCHIECTASIS

DR. SMITH: We're going to start with a case study that's going to be a two part case study for developing inhalational therapies for non-CF bronchiectasis. First part will be about patient selection and trial duration and the second will be endpoint considerations. First up will be Peter Kim from FDA.

PART I: PATIENT SELECTION AND TRIAL DURATION

DR. KIM: Good afternoon. I'll be presenting the first part of this case study on developing an inhalational therapy for non-cystic fibrosis bronchiectasis.

So company A wants to develop drug Y to reduce

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the incidents of exacerbations due to bacterial pathogens in patients with non-CF bronchiectasis. They are trying to identify a patient population that's most likely to demonstrate a treatment benefit in their trials. But they are aware of a number of issues: no anti-bacterial drugs are currently approved to reduce the incidents of exacerbations due to bacterial pathogens in patients with non-CF bronchiectasis, previous trials of inhaled anti-bacterial drugs have failed to demonstrate benefit over a current standard of care, and there are uncertainties regarding an appropriate trial design.

They know that non-CF bronchiectasis patients are a heterogeneous population with different etiologies for their disease; severity of illness and comorbid conditions in these patients vary; and the incidents of exacerbations may vary even within an individual patient over time by season and potentially by region of the world.

And there are additional factors. A variety of microorganisms may cause exacerbations, not just bacteria. And they're wondering how to deal with

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patients with the following, such as a history of nontuberculous mycobacteria pulmonary infections and also patients with allergic bronchopulmonary aspergillosis.

They also know the patients -- these patients can be on a number of concomitant adjunctive therapies, and some may require maintenance systemaic corticosteroids. Should they include these patients in the studies or no?

So as far as selecting the patient population most likely to show a treatment benefit, they want to enroll patients with multiple exacerbations in the prior year. However, they also know that patients enrolled in previous trials tended to have fewer exacerbations during the trials than in the prior year.

Should they only include patients who required hospitalization during one or more of these prior exacerbations? And what criteria should they use to define a prior exacerbation? Should they only enroll those patients who are on concomitant macrolide therapy or should they stratify enrolment based on macrolide therapy? Should they only include patients with multi-

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lobar involvement? Are there other demographic or disease-related factors? And then also what patient characteristics or comorbidities should lead to trial exclusion?

Additionally, they're thinking about the duration of the phase 3 trials. They note that prior phase 3 trials lasting a year may not have been long enough to adequately assess whether the new study therapy reduced the frequency of exacerbations to a clinically meaningful extent and whether the treatment effect will be durable beyond a year. But they also know the practical considerations of conducting trials longer than a year: cost, and also that it may not be ethical for patients to stay on placebo for a period of 2 or more years.

Another option could be to consider a study which includes an open-label extension period to address ethical issues relating to the extended use of placebo. However, they're also aware that such a trial design would not be as informative as a randomized trial with a 2 year evaluation period. Additionally, potentially longer trials could assess for additional

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safety issues with chronic use and the developmental of bacterial resistance.

So the questions to the panel: one, how would you advise company A to enrich their trials for subjects most likely to demonstrate a treatment benefit? And two, what is an appropriate duration for the phase 3 trials? Thank you.

DR. SMITH: Thank you, Peter. Next will be LaRee Tracy from FDA to discuss endpoint considerations.

PART II: ENDPOINT CONSIDERATIONS

DR. TRACY: Okay. Hello. So the good news is this is the last presentation. The bad news is it's given by myself and I'm a statistician, so I will perhaps lose a few of you in a few of my slides, but please bear with me.

So thanks to the organizers for having this interesting workshop and I also wanted to just thank the patients for coming and providing their perspective. That takes a lot of courage and it's always helpful from my point of view to hear your story in trying to understand how to design these trials. So

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thank you.

So as has been discussed throughout today, the considerations for trial designing endpoints specific to non-cystic fibrosis bronchiectasis really have to be superiority trials because there is no approved or current standard of care for treating this patient population. And as has also been discussed and nicely outlined in Dr. Tino's presentation is that the key goal in management of this disease is the reduction of pulmonary exacerbations, because those are the major driver for complications, increased healthcare cost, decreased quality of life and significant morbidity.

So then that leads us to: What's the overall trial objective for a future clinical trial for non-cystic fibrosis bronchiectasis? There's just a few thoughts here. We'll discuss in our panel discussion. It would perhaps include reduction of exacerbations or would it be reduction in hospitalizations, however that's defined? Or could it be decreased time on antibacterials or a combination thereof or something else?

But clearly given that whatever product is

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evaluated, will be given or taken chronically over perhaps decades. So that then leads the need for rigorous evaluation of this treatment over a sufficient length of time, which is Dr. Kim just outlined. We'll discuss that in a few moments.

There's been some discussion about the use of the time to first exacerbation endpoint. This has been -- this served as the primary endpoint in several previous clinical trials for this indication. It's a relatively parsimonious endpoint, I mean, relative to other endpoints because it's an easy one to analyze. Essentially, we're looking at the first event and only the first event and how long it takes to get there.

However, as we all have discussed and understand, it ignores all the subsequent events that occur after that first event. And for a chronic disease such as non-cystic fibrosis bronchiectasis, we are interested in what's happening in the course of that patient's life with that disease.

Therefore, this endpoint is often -- can be often easily misinterpreted. For example, a delay observed in the initial exacerbation in one arm versus

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another in a treatment -- a clinical trial may be followed by more or -- more exacerbations or more -- severe exacerbations, but aren't captured in that endpoint.

And then finally, despite the fact this endpoint has been used and it's relatively easy to use, the results from prior clinical trials have been rather inconsistent and there's no evidence at the current time that time to first exacerbation predicts long-term clinical outcome for this patient population.

So now I want to just talk a bit about considerations for other clinical endpoints in future clinical trials for non-cystic fibrosis bronchiectasis. And the first being one of total pulmonary exacerbations during the trial; total comprising first and recurrent events. This is often described as the frequency endpoint.

Another endpoint for discussion or consideration would be the clinical severity of exacerbations, which of course would need to be defined, but could be perhaps the duration of exacerbations, average duration of exacerbations that

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is. It could be the average duration of hospitalizations for exacerbations or days on IV therapy or a combination of those endpoints.

So then you could imagine perhaps taking the total pulmonary exacerbations endpoint along with the clinical severity of exacerbations, however defined, and creating a co-primary endpoint, which I'll discuss a little bit more in a moment.

Now, with respect to the frequency of exacerbations endpoint, there's some considerations I want to highlight. So in some cases, pulmonary exacerbations are less frequent, but more severe and prolonged, and this endpoint doesn't capture that. Nor does this endpoint capture the patients at risk time, such that while a patient is experiencing an exacerbation, he or she is not presently at risk for experiencing another one.

And in addition, investigators may have varying opinions as to when an exacerbation has ended as well as its severity. However, I would submit that that could be addressed to some degree in the protocol design.

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So when analyzing the frequency of exacerbations endpoint, which we've done in the past as a count, the strength of this approach is that it captures all exacerbations. And when modeled, you can incorporate other characteristics and factors and it generates an estimate of the mean.

However, as I said, the weakness of this endpoint is it doesn't capture the patients at risk time. It also fails to account for correlation between or among events for the same subject.

So now I want to just discuss another way we can think about analyzing or capturing the course of the patient's experience during a clinical trial, which would essentially be done under the auspices of a recurrent time-to-event approach.

This is essentially a modified Cox proportional-hazards model. It generates an estimate of the risk of recurrent events. And this isn't a new approach. It's been -- these approaches have existed for quite some time. And two prevailing approaches exist that could be considered. The first is called the Andersen-Gill model, which analyses time between

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events, which is defined as the gap time, but that's not really that relevant right now. It analyses that in an independent way. These models can also include time-varying covariates to account for correlations. And the beauty of that is we could model how an exacerbation is treated during the trial as a time-varying covariate in our models.

It assumes, however, though that the events are of the same type and the same nature and it assumes a proportionality. So that can be a false assumption potentially for this disease.

And then the focus and the purpose of the use of this is when we're interested in the overall effect on the intensity of the occurrence of a recurrent event.

So a similar approach is that by Prentice, Williams and Peterson, which is essentially a modified Andersen-Gill, which analyses gap times using conditional risk sets, but it doesn't assume any baseline hazard assumptions. And it's used when we're interested in if the occurrence of the first event increases the likelihood of a recurrent event; that is

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risk of a future PE if it's impacted by the prior PE. So both of those approaches could be considered in the design or the analysis of an endpoint in a future clinical trial.

And then really briefly I want to discuss the consideration for a co-primary endpoint which would incorporate both total pulmonary exacerbations as well as severity of exacerbations, however that's defined. Of course, the beauty of this is it would capture two important clinical endpoints. Of course, the challenge or the thought would need to go into the necessary sample size to power on both of those endpoints.

However, if it's true -- and I think that the epidemiologic data are still needed -- but if it is true that the prevalence of this disease is increasing and it's likely driven by the increasing age in our population, then potentially there are adequate number of patients to study.

And then finally, I want just to discuss pulmonary function and the quality of life measures because those have been discussed a lot and it is important to mention them in the context of non-cystic

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fibrosis bronchiectasis because they haven't been ignored endpoints. However, they have not been highly sensitive endpoints.

Throughout the prior development for other products that endpoints have been explored for quality of life, either the quality of life B or the SGRQ, and neither of those PROs was sensitive enough, didn't show a statistically significant effect.

And specific to the ORBIT trials, as one of the patient speakers earlier mentioned, that endpoint was evaluated at week 48. However, that endpoint or that data were also looked at over time in those trials and did not show an effect.

And with respect to pulmonary function, the same story unfortunately exists, that is there's no -- has not been a difference observed on pulmonary function, a change in pulmonary function from baseline among the ORBIT trials and the RESPIRE trials.

So then I just leave you now with our questions. The first being -- the first two were already highlighted by Dr. Kim. So then the questions that I have with respect to the endpoints are for us to

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discuss the importance of the non-time to first exacerbation endpoints. So I think it's pretty well thought that time to first exacerbation isn't enough.

And the next question is or point for discussion is: Is a co-primary endpoint of total exacerbations and severity of exacerbations clinically meaningful? And the last is: What other endpoints should we consider? Thank you.

MODERATED PANEL DISCUSSION (WITH AUDIENCE Q&A)

DR. O'DONNELL: Great. Thank you very much. So we'll go through these questions, just as Patrick did, sort of one by one. I do want to say how I think it's really great that we have the CF and non-CF community here together, because I think we in the non-CF world have, you know, frequently lamented the fact that our studies that have been modeled after CF trials haven't worked very well. So we need some advice here.

So let's start. How can we enrich the trials to demonstrate a treatment effect? I think, James, do you have a comment there?

DR. CHALMERS: I mean, I think the first thing is to look at the trials that have just been completed

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and ask why did we -- why did we not see consistent treatment effects. I mean, one of the striking findings there was in the RESPIRE 2 study, 68 percent of patients didn't have any events during the trial. So regardless of any other aspect of your trial design, if the study is underpowered, we won't able to demonstrate an effect.

So the first thing should be how do we enrich for patient -- if we're going to have an exacerbation endpoint, which I think we've all agreed that a preconceived exacerbation endpoint is either the primary or a co-primary, how do we increase the number of events?

And Greg showed a slide with one of the recent studies that suggest that patients that have two exacerbations are quite an inconsistent group. So some of them will have future events. Some of them have no events in the following year. Once you raise the bar to three or four, you see a much more consistent phenotype of patients that will always have events. That's been demonstrated in CF, it's been demonstrated in COPD, and it's been demonstrated now in several

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studies in bronchiectasis.

So I think a starting point would be to say we need more patients with more exacerbations. And then there are additional factors like limiting just to pseudomonas seems to increase the likelihood of events because those patients are more at risk of exacerbation. So as a starting point, we need to think about how do we get more events in order to have trials that give positive results.

DR. O'DONNELL: Yes. Susan.

DR. ELLENBERG: So with regard to the comment before that, "taking in people who had multiple exacerbations in their previous history always had fewer when you actually did the trial," that's always to be expected. I mean, that's the standard regression to the mean problem.

But as was just said, still people who had more exacerbation -- even if they have less in the first year after than they had in the year before, they're still probably going to have more than people who had fewer exacerbations in their history. So that shouldn't worry people that, you know, that they had

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fewer in the trial than they did before.
DR. O'DONNELL: Jeff.
DR. ALDER: For the first question, I would advise the company first to figure out what the medical benefit is. And we've fixated on exacerbations during some of our rehearsals. A big critique that came is: "You're not measuring what patients complain about."
You're on a 365-day a year disease; a therapy that's cyclic, on off. And yet we're trying to boil this down to an event that happens maybe once a year and the time or the frequency of that. And that seems like it's a very dull instrument and we're losing a lot of data.
And as one example, in one of our PROs, we measured at the end of on and off cycles with the SGRQ. And we found, lo and behold, the differential is greatest at the end of on cycle. And by the time we get to the end of an off cycle, there's virtually no difference. So sure at 48 weeks there's no difference in the PRO scores, but if you totaled up all the differences they're enormous during the trial, but not at the beginning and end.

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So I feel that exacerbations may not be the way to go. It's too infrequent. And I don't care if you start with two or three or what. You're going to get fewer than you think. And it's really not capturing the nature. It's trying to make a chronic disease fit into an acute model, where you look at a cure or a lack of cure after 5 days therapy. This is much different.
DR. O'DONNELL: Other comments about that? Yes.
DR. FROEHLICH: I have a feeling that for clinical trials when you count the number of exacerbations in the previous year versus the number of exacerbations that you proactively observe in a clinical trial, you are comparing apples and oranges. I think -- I personally believe for future trials we need to do a better job to really nail down how many exacerbations a patient had before he or she enters a study.
I think it's easy to count one or two exacerbations that as per the trial definitions were not an exacerbation. And if you spin this even further

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-- and this of course makes the study much more onerous -- you would have to observe patients for a run-in time before you enter them in a trial. But I think it's critical for -- when you go for exacerbations as one of the primary endpoints, that you need to make sure that the number of exacerbations is similarly assessed before the study versus during the study.
And we see often in phase 3 trials and other indications that the phase 3 event rate is lower than phase 2 event rates. I can see that. But in this particular situation, I think the counting of previous exacerbations may play a critical role.
DR. FOLLMANN: Well, I guess I'd agree with that, but I think exacerbations is a legitimate endpoint and we want to enrich for a patient population that will have a lot of exacerbations. And so we want to have some period of run-in or, you know, a history of them so we can select patients that have more endpoints during the course of the study.
And just to make another plug, earlier I brought up the idea of a crossover trial. I think that would also be a fair thing to consider here. You could

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have a 2-year study, with a year of placebo followed by a year of drug or vice versa.
And here this heterogeneity we've been hearing about during the course of the discussions, including this regression, the mean phenomenon, which is a reflection of heterogeneity, the crossover design sort of benefits from heterogeneity, the more the heterogeneity, the more efficient the design is.
So that's what I would recommend, you know, a sponsor to do, enrich the study. And you have data on this, so you could, you know, see what potential gains there are with a crossover trial of 2 years duration.
DR. SMITH: I will say that in response to Dr. Froehlich's comment, we've noticed with this indication and with other frequently recurring indications that there's often not very good documentation of what the previous history was of the exacerbation. And I'm not sure how you can go back a year and somehow provide adequate documentation that somebody met the same kind of clinical criteria that you're going to be using to define an event after patients have been randomized.
DR. O'DONNELL: Yeah, I'll just say -- I mean,

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I was on the Adjudication Committee for exacerbations for one of these trials and it was extremely tough even within the trial to adjudicate. But you're absolutely right. I mean, how we define an exacerbation pre-enrollment was different than how it's defined once you're in the trial.

And now we've come up with the definition from the -- Greg mentioned from the -- published in the ERJ. But that's not really going to help us. So any other comments would be appreciated.

DR. ZEITLIN: I have a question about heterogeneity. In seeing that CT scan for the 77-year-old where an entire lung is cystic and hearing from patient representatives they might have a focal area that's a problem, how do you know your inhaled antibiotic is penetrating the area that would make the most difference to time to exacerbation? So I'm wondering if you can control for that sort of variability in where the disease is attacking the lungs.

DR. O'DONNELL: Any comments on that? Alan?

DR. BARKER: (off mic) how far down -- in

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diffused bronchiectasis, we're not even sure how far down the drug goes. We like to think that it gets down. But you're probably right that in -- somebody with a unilateral or one lung, most of it is going to go to the good lung. I mean, it's about --

DR. ALDER: Yeah, I would -- we have some scintigraphy studies that show great distribution, but those are normally done in healthy volunteers, not people with impaired lung function. So now it gets very complicated with the consolidations and does drug penetrate or not. That's a big variable.

DR. TINO: Well, can I just comment about the distribution of the antibiotic? I mean, what we have as a pretty good surrogate is micro data. I mean, you can see when the patients are on drug, colony forming is dropped; when they're off, it goes up.

And so if you're reducing total bug burden, some of the stuff that James has shown, I think that's a surrogate for distribution of the drug in killing bugs. And whether the active infection is in one area or not, I don't think we're ever going to be able to measure that. But I think the surrogate is the micro.

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DR. ALLENDE: Yes, I wanted to comment that I agree with the point brought by Dr. Froehlich. There was a lot of heterogeneity in the way that the number of exacerbations were considered for the inclusion criteria and then during the trial. And there was, as Dr. Smith pointed out, a lack of documentation. And I have to add that there was lack of documentation also on the anatomical characteristics, like we didn't have much detail about upper lobes or distribution of bronchiectasis to make some kind of more complete assessment of what happened with the absorption, the bioavailability of the drug. So there's a lot of data that needs to be collected to make a better assessment.

DR. O'DONNELL: Dr. Noone.

DR. NOONE: Just going to say, we're talking about heterogeneity here a lot. And just going back to the radiology point, I don't know if there are data on this, but I certainly had many patients who have quite mild changes on the CT imaging -- I bet we all do -- and yet have disproportionate symptoms to the radiologic changes and vice versa. I have some people with quite marked changes and sort of do okay.

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So, you know, the radiology is all over the shop. I mean, it gets away a bit from the physical penetration thing, but trying to think about heterogeneity and differentiating patients, I'm not sure -- and it probably will be logistically very difficult anyway. But the radiology really is very all over the place.

DR. O'DONNELL: James?

DR. CHALMERS: I would just back that up. I would really not get into a discussion about the radiology of bronchiectasis as multiple studies have looked at this whether radiological appearance predicts clinical phenotype or predicts exacerbation frequency or predicts response to drugs in different contexts and they show no real correlation between radiological extent of disease and anything clinically meaningful.

You can have patients with very mild bronchiectasis radiologically who are incredibly sick and you can have patients that have completely destroyed lungs, like the ones that you saw with Dr. Tino, particularly in the context of things like post TB change, and the patients are almost asymptomatic.

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And so it's very difficult to take anything radiological and think you're going to make anything clinically meaningful out of it.

DR. BARKER: On your question about enriching, it's not as robust as previous exacerbation, but FEV1 or the level of FEV1 has some relationship to exacerbation; that is somebody who has relatively normal FEV1 is going to have fewer exacerbations than somebody that has 30 or 40 percent FEV1.

The studies that we've been talking about, the aztreonam and two cipros, the azteronam didn't have an upper limit of FEV1 and the cipros had 80 or 90 percent. I would suggest that we for enriching consider lowering the upper limit of the FEV1. You can't make it too low, 40 or 50 percent, you won't get the patients. But I would think your ceiling should be something lower than normal pulmonary function, which is 80 or 90 percent. And I would at least consider 50 to 60 percent or something.

DR. O'DONNEL: So maybe James and Greg could comment on that because you have this paper just coming out about this issue.

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DR. CHALMERS: I mean, the Bayer studies did some sub-analyses of above 50 and less than 50 and there wasn't really any convincing difference across the four different analyses to say that one lung function level is better than another lung function level.

So again, I think Alan's point is right, you want to enrich for people who have had more events. So by asking for people with a history of three or four exacerbations in the previous year, you'll get more of the patients with lower lung function.

But remember that with inhaled antibiotics, we always cut out people with less than 30 percent because we don't want to put them at risk of bronchospasm. So if you set that bar at 50 percent and then the lower bar at 30, you're really not going to be able to do a feasible trial. So again, I would go back to exacerbations and not lung function.

DR. TINO: Yeah, I agree.

DR. O'DONNEL: So we agree that three or more exacerbations defined in some fashion would help to enrich further trials? Patrick.

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DR. FLUME: You know, part of the problem is that we describe this group as non-CF bronchiectasis and we have to stop doing that, because bronchiectasis patients of which CF patients are one endotype and then there are others, and really, you're getting at what is the phenotype because there are patients who do behave much like CF patients. There are patient who actually benefit from pulmozyme.

I would venture to guess -- so we'll make everyone raise their hands -- that every clinician in here who takes care of bronchiectasis patients has patient on inhaled antibiotics and believes that it's working well for them. So we use them. We try them. And as you know, we've published our data. I've long complained about the phenotype we looked at in the AIR-BX studies. Those patients looked like they had COPD, because they had a high utilization of long-acting bronchodilators, inhaled steroids and they had low use of hypertonics and they had chronic macrolides. As Greg showed you, those were the opposite direction of recommended therapies.

There was some improvement in the Bayer

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studies and the Aradigm, but the other part is they went into countries that enrolled patient who don't have the same access to care. And so you start to wonder what was that doing to the dilution of your population.

So the answer isn't doing a (inaudible) work in these patients. I believe they do. It's about finding out the right population and whom they're going to benefit, who can demonstrate that benefit. And you've got to find a way to enrich them.

The risk that we had is, those studies had to be so large that finding those patients is what made those companies go out into areas or broaden their inclusion criteria to make them get -- you know, finish in a timely manner.

DR. O'DONNEL: One other -- sorry, one other caveat is trying to enroll patients with three or more exacerbations who are not on off-label inhaled antibiotics at this point. That's the challenge to try to stop somebody ethically that is on -- Susan.

DR. ELLENBERG: Yeah. So I was intrigued with a comment somebody made at the beginning of this

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discussion that maybe somebody with -- having one exacerbation a year, maybe that's not really the most important thing for patients because with they live with this disease 365 days a year.

Now, somebody who has got -- who is having three or more exacerbations every year, maybe that is quite a meaningful thing. But I -- I'm interested to hear what, you know, maybe some of the patients here have to say about what endpoint would be of most interest.

MR. ZIMMERMAN: One exacerbation is terrible; that's the bottom line. I don't want any exacerbations.

DR. ELLENBERG: So if you were on average having one exacerbation a year and a treatment would reduce that to maybe only one every three years --

MR. ZIMMERMAN: Sign me up.

DR. ELLENBERG: -- that -- okay.

DR. SMITH: Yeah. There you go.

MR. ZIMMERMAN: It's quality of life; that's what it comes down to.

DR. SMITH: Are there any specific quality of

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life issues or other things besides, say, an actual exacerbation that you might find beneficial?

MR. ZIMMERMAN: I think Mary can answer this better than me.

DR. SMITH: Well, we could hear from both of you.

MS. KITLOWSKI: All right. Well, could -- I'm sorry, could you repeat your question?

DR. SMITH: So the question is, besides reducing the frequency of exacerbations what other types of outcomes would be important to you.

MS. KITLOWSKI: Well, to me would be even reducing the time of the exacerbation. So like you said, one exacerbation is bad enough, but if -- you know, when I go on IV antibiotics, I can be on them, you know, for 4 weeks. And, you know, patient confession here. I tend to like try to push it off as long as I can. So I've been feeling pretty bad for a while leading up to that.

But if there were a way of cutting that down to even, you know, just 2 weeks where we're not incapacitated, where, you know, we're still able to

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work, I mean, that would be a huge improvement.

But I just -- you know, I wanted to second also just -- you know, even reducing one exacerbation would make a huge difference. You know, quality of life --

DR. SMITH: So if there was some way of capturing the severity of an exacerbation and that could be improved, that would --

MR. ZIMMERMAN: Yeah, severity I think is really important. If I don't have to get to the IV antibiotic stage, great. If I just feel like at the top my chest and I can do something quick to get rid of it, even better. Time and severity are really important. And we're going to have exacerbations, but let's reduce the frequency and let's reduce the severity.

DR. FOLLMANN: So a question related to that. Wouldn't you be indifferent between one exacerbation, say, of 4 weeks versus 2 exacerbations of 2 weeks -- what would be worse or would they be same to you?

MR. ZIMMERMAN: I'd probably say it's about the same just because it's the same time. And being

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sick is being sick whether it's for 2 weeks at a time or 4 weeks overall.

DR. O'DONNEL: Mary.

MS. KITLOWSKI: Sorry. If I could just chime into that. I would say it also depends on the nature of the treatment, because if I'm on IV antibiotics and I have to go -- I'm on IV for 2 weeks, then, you know, PICC line is gone and then I get another exacerbation for 2 weeks. I mean, that's a lot to go through getting the PICC line, you know, IV and twice. So, you know -- so my answer is sort of a caveat there. I mean, yeah, 2 weeks sounds great, but, you know, there's the extra consideration.

DR. ELLENBERG: So then another possible type of endpoint would be the number of days over a year that one is -- in which one is experiencing an exacerbation.

DR. CHEN: So I've a question for our patient representative, Jasan. It's that it seems to me that you're talking about the impact, the severity related to the patient. But I'm interested in all of the outcomes, say -- that you mentioned about quality of

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life. Is that quality of life just directly related during exacerbation or quality of life for the -- I mean, even in the stable state, if I can call it as stable. You know, like symptom severity, you have higher symptoms. That when you are not in exacerbations, that it's actually also impacting your quality of life? And what other things that you consider as quality of life, like symptoms, the impact in your working ability, your daily life, things like that?

MR. ZIMMERMAN: That's a great question and I think it comes to the variability of the disease. For me, where I'm in my progression, exacerbations are my main concern. And I don't know that that's true for everybody. It could be that -- and where's Mary? I want to know what you had to say too.

It could be that, you know, maybe somebody is not actively sick, but still doesn't feel like the lung function is there and so that's impacting daily life, working or whatever, or there are other cough symptoms that are just taking over. For me that's not as big of an issue, but who knows what's going to happen down the

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line.

DR. CHEN: So follow-up would be, if there's a treatment that attacks those symptoms, would that be important to you -- if there's any treatment that may not reduce the number of exacerbations, but actually make you have less of those symptoms during your stable stage, normal days?

MR. ZIMMERMAN: Sure. And also, kind of what Chip mentioned today, you know, he takes two and a half or three hours a day. If I don't have to do that, if it can be something that's easier to do that doesn't take as much of my day, because that's also quality of life right there.

MS. KITLOWSKI: Yeah. So, you know, part of it is I think the severity for individual patients. I cough a lot, you know, and I can have bronchospasms. And even though I always coughed, it has gotten worse, as, you know, my lung function has declined. So I think part of that question just depends on the severity for the patient.

For me now, you know, I feel like -- you know, you see me on oxygen. So I -- it's like a continuous

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quality of life. You know, lower quality of life is pretty much ever present for me at this point. When I -- you know, 20 years ago, you know, quality of life was great. I might just get, you know, sick a couple weeks out of the year. But other than that, it was great. So I think, you know, again it depends on the severity for the patients.

DR. O'DONNEL: Jeff.

DR. ALDER: Yeah. Regarding the PROs -- you might as well state (ph) the microphone -- the approach we're using now is, relatively speaking, lots of questions, but administered relatively and frequently with three call periods of 7 days or even longer. And again, we've heard patients say that's not capturing how I'm feeling, that we're missing a lot of patient input.

And what's been suggested is something like a daily electronic dairy of -- something simple, five questions maybe, because we're missing a lot of input by throwing 150 questions once a month at a patient. "How would you perceive that?" You know, something with a daily input to capture the waxing and waning.

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MS. KITLOWSKI: I think that has a lot of merit. When they were setting up the PCD, working on the PCD questionnaire, I talked with -- I'm assuming it was Dr. Quittner's team in Florida. They were asking me some of the questions. And when I shared with my husband later how I answered -- they caught me on a good day, so I was like, "Oh, yeah, things are pretty much good, you know." And he was like, "Well, how about, you know, a few weeks ago when you had to go downstairs? You kept having to leave the bedroom because you couldn't sleep because you were coughing too much." And I was like, "Oh! Yeah, I kind of forgot about that."

You know, so -- yeah, I there is definitely merit to that because I have good points during the year. In the fall when my symptoms start flaring up, I -- you know, I measured it after he mentioned that, and September and October I spent about half of my time up late at night not able to sleep because of, you know, all the coughing and having trouble.

So I think having it on, you know, a daily basis would be a better capture and particularly when

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the survey -- the QOLB right now only does a 7-day recall.

DR. O'DONNEL: Tim.

DR. AKSAMIT: Yeah. So which is --

MR. ZIMMERMAN: Yeah, I agree with that.

DR. AKSAMIT: Okay.

MR. ZIMMERMAN: I think the monthly is a snapshot. And if it' daily, then you get a much better sense of what it's like. And it could also be the time of day too. That depends on how good you're feeling that day or not. But I think it's a much better course of how you feel.

DR. O'DONNEL: Another comment from the audience?

UNIDENTIFIED SPEAKER: (off mic). I just want to make a couple of observations. One of them is the goals Cayston study and in the ciprofloxacin DI study, we observe that when the quality of life questionnaire was measured around the time of an exacerbation, there was a much bigger decrease in the quality of life of those patients than during the sort of stable state. So there is no doubt that at that time of an

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exacerbation, at least in my mind, there is a big drop in quality of life.

The other point that I wanted to make, which is very interesting -- I mean, it's absolutely true -- if you want to have the number of exacerbations as your endpoint, you have to take patients who've got all exacerbations. That is obvious. The problem that you find in practice -- and I've been involved for 11 years enrolling patients into these clinic trials -- these patients are very rarely eligible because they've got so many exacerbations per year.

So the question then is how quickly can you enroll a study, you know, with a reasonable number of patient and how big a quantum of evidence can you really produce given the small number of these patients, because they're almost never eligible because they continue to have exacerbations so they're on some antibiotic therapy because of that. So there's a practical problem with the size of these studies.

DR. FOLLMANN: Sort of a clarification question. You say that these patients who have a lot of exacerbations are not eligible because they have too

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many exacerbations? So I'm missing something.

UNIDENTIFIED SPEAKER: Well, if they are -- you typically exclude patients who have been on antibiotics over the last 28 days --

DR. FOLLMANN: I see.

UNIDENTIFIED SPEAKER: -- or some period of trial -- some period of time, because then you really have a population that is so variable due to the previous treatment of the antibiotics. So it's difficult to enroll these patients.

DR. FOLLMANN: So you exclude them because they have had recent antibiotics and you think that muddies the water. Though -- you know, you randomize them to the two arms and then, you know, you still could see a difference or not. I mean, it's still a fair comparison. But --

UNIDENTIFIED SPEAKER: Well, it would be an interesting -- I mean, the other thing of course, if you wanted to have pseudomonas at the time of entry to the trial, again, if they have been on antibiotics or not -- the antibiotics for the last 28 days, it is quite possible that will you not find any pseudomonas

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in their sputum. So there are some real practical difficulties.

DR. FOLLMANN: But if they had sort of a history of pseudomonas and now they got antibiotics for 28 days and the pseudomonas has gone away, it might well come back and they still might be a good candidate for the trial.

DR. O'DONNEL: Okay. Tim Aksamit has been waiting.

DR. AKSAMIT: Yeah. Okay, good. So I would just follow that up, that signal-to-noise ratio that we've been reconciling, that most patients have shared with us and myself as a clinician that the goal is zero exacerbations.

But from a statistical standpoint, I think it would be incredibly tough if somebody is having one every year or every other year, which is too much for sure clinically in the purposes of a phase 3 study to, say, try to demonstrate impact or event rate for that infrequent, and again, to be in alignment.

So then you raise the issue of: Are there other possibilities? And we understand that there is

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some data that when individuals have an exacerbation, they have symptoms for up to 2 weeks before the time period and then 5 weeks after the time period. And so if you had days of exacerbation rather than event rate, that that they may scratch at some of this. And so if we start thinking about different endpoints or trying to get more signal and less noise, that may be an opportunity.

And then the other opportunity -- and I would ask James, because I don't know that there has been data to know what happens between exacerbations and has there clearly been studies to look at quality of life measures and some symptom scoring in between exacerbations for those people, even though you in between exacerbation say you feel well. But are your scores if you're having more exacerbations in between your exacerbations different than somebody else with less frequent scores?

And that may be the opportunity to try to enrich the signal rather than the noise to try to then pick up on this rather than use just events. So I think we continue to be a little bit off the mark of

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using just the even rate as the only marker here.

DR. CHALMERS: So just to come in on that. I mean, there has been one study that looked using electronic diaries in bronchiectasis that did show that 20 percent of patients with bronchiectasis never recovered to the same level in terms of symptoms after an exacerbation.

So many patients experience a drop in lung function. All patients experience a drop in quality of life. Most return to close to baseline, but about 20 percent never recover. And that's again consistent with the biology that you see in CF and in COPD, where exacerbations cause gradual decrements in quality of life and lung function over time.

So an electronic diary would be fantastic to capture some of that data. The difficulty is there's no validated diary at the moment in bronchiectasis. So if we're answering question one, "how would you advise company A today how to do a trial," it would be difficult to say use this diary or use that diary because there isn't a validated one in bronchiectasis.

DR. AKSAMIT: Well -- and the idea here is not

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just to look at the delta change in the quality of life measures, whether it's QOL-B or St. George's, but to use absolute numbers over that period of time to try to capture exactly this for the more symptomatic patients. Even though you say, "Well, I feel well; it's a good day for me," but your good day is a really crummy day for somebody else, relatively speaking.

DR. O'DONNEL: So I think we're saying it's some combination of number of exacerbations and symptom burden day to day that has to be factored in. Because I think my -- what I hear from patients -- I may have many patients who have one exacerbation a year and are essentially asymptomatic the rest of the time and I'm not sure they would be as inclined to do a chronic therapy as somebody like Mary or Jasan.

So why don't we move to question four. Since we're talking about the endpoints, thoughts on co-primary endpoint. Oh, I'm sorry. Angela.

DR. DAVIS: Thanks. Hi. Angela Davis. I'm with Grifols. So one question that may be -- might be directed towards James or the statisticians -- I mean, obviously -- Anne, I do think we're kind of saying the

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same thing that it's a composite or even thinking of a composite score. But I wonder if there has been any thought put into looking at going back to why some of these trials have failed and developing some propensity score, some matching in order to identify specific phenotypes of patients to then develop composite scores as an endpoint for what's a successful study to look like?

UNIDENTIFIED SPEAKER: The thing is not working.

DR. TRACY: So with respect to the ORBIT trials, the Bayer -- or, excuse me, the Aradigm trails, so -- you know, part of the challenge was, as was mentioned, that there were limited pre-randomization data that would have been really useful to understand the underlying etiology of the disease for these patients as well as the affected lobe.

So that was -- those data were just simply not there along with the fact that -- because of the inclusion, exclusion criteria and the prevalence challenges, these trials are global, so we have tremendous heterogeneity across the globe and what a

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NCFB patient looks like in the United States is different than that in Japan. But again, we're not getting any other data other than region. Yes, so we don't have that phenotype, genotype level of data to really understand what's going on.

I think your question about propensity score models is an interesting one, hadn't thought about that. I suppose you could do it, but you'd have to pool all the data from the various trials because you -- I don't know if you know a lot about propensity scores, you must -- since you asked the question. But you need a sufficiently large number of observations to model the counterfactual estimate for the propensity score.

But I still think that's worth considering. You know, I think this is an effort that needs to happen with or without a current trial. We need to be mining the existing clinical trial data. We need to be collecting more robust epidemiologic natural history's data globally, not just in the United States considering the fact these trials are going to be done globally, you know, and learning as we go.

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So thank you. I like that question. And, you know, no, we haven't done that, but I think it's something worth perhaps academics and others can do. If they want to give me some time off, I'll do it. But I don't know.

DR. O'DONNEL: James, answer the question?

DR. CHALMERS: Yeah. So I'm not going to comment on propensity scores particularly after a statistician has just gone into that. But what the question is dependent on is the company sharing their date with academics so that we can answer these questions. And I think the patient would agree that if 1,000 of patients have given their time to do these studies, we need to learn as much as we can from them.

We've been fortunate that some companies have shared their data from previous failed trials. So Gilead, for example, have provided us with access to the aztreonam trial data. And we'll present a poster at the World Bronchiectasis Conference next month, where we have identified a population that responds in both AIR-BX1 and AIR-BX2 with quality of life improvements above the MCID simply based on their

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baseline bacterial load. So the patients with the highest baseline bacterial load had massive improvements in quality of life, whereas those that had very low bacterial burden had no response at all.

So that's a very simple biomarker that certainly in that trial seemed to predict response very robustly across both trials. And so that's something that could easily be tested in other studies to validate that concept.

DR. O'DONNEL: Patrick.

DR. FLUME: So I wasn't going to comment on the risks or benefits of a co-primary, but comment about severity and duration. This is something we've grappled with in the CF world as well and it's complicated by how treatment decisions are made and the variance in clinical practice.

So although it might seem intuitive that a person that's hospitalized is having a more severe event than someone who just gets home IVs or gets oral antibiotics, but frequently those decisions are based upon which pathogen they're treating. If you're treating staph, you have oral opportunities; and if you

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have pseudomonas, you have fewer opportunities. And sometimes hospitalization decisions are based upon resources available to the family or your past history that there's just no way you're giving this person therapy at home. So it has zero to do with physiology.

In terms of duration, the reason -- one of the reasons we're doing a duration of treatments study in CF is because the variation in practice is enormous. So the decision of whether someone gets 7 days, 10 days, 14 days or 28 days has little to do with anything except the perception of what that particular patient needs and often times is a function of the calendar as opposed to some other marker.

What we do know, and Tim has already mentioned this, is in the CF population where we've done the analysis looking at quality of life parameters after an event occurs, that for some of those parameters, particularly the physical functioning parameters, take 6 weeks to resolve, whereas respiratory symptoms will resolve within 2 weeks.

And so when you talk about, well, when is the exacerbation over, it's typically the start and stop of

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antibiotic days and yet the patient remains symptomatic. And that's excluding what Tim already talked about, was the duration of symptoms before a decision was made to treat.

DR. O'DONNEL: Greg.

DR. TINO: I want to echo what Patrick said, just add a couple of things. You know, I think the idea of a co-primary endpoint would be great if we had some guidance about definitions and things like severity. So we don't. And to echo what Patrick said, but also -- you know, many of the clinical trials -- most of the clinical trials are international. To try to enrich is really the goal than to recruit patients from other countries.

And so, for example, if you use hospitalization as a measure of severity from across countries, in our institution I can give home IV antibiotics. In the UK, the move to IV antibiotic requires hospitalization, whether that really speaks severity or just speaks to the fact that resources are limited in terms of home IV antibiotics. That's not only a national problem, but an international problem.

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So I'd love to be able to assess severity of exacerbation and reduce that, but I don't know of any other measures that could be good surrogates that can be studied.

DR. CHEN: Actually, I may be able to answer this -- the question that related to your comment about there's no validated patient-reporting outcomes. There's an instrument called the EXACT-PRO. It was designed to catch underreporting as to the patient -- for COPD patients and it actually has been qualified by FDA COA -- the Drug Development and Tools as a exploratory endpoint to use. And so maybe that tool, the EXACT -- and it also has this symptom subscale, maybe able to modify it for the pancreatitis patient populations.

DR. AKSAMIT: And I might just follow-up I think on Dr. Tracy's comment about some of the heterogeneity issues. I think that we also need to understand internationally -- we don't know for sure that individuals on one continent are different than another continent, but what we don't know is what the definition is. And so I would just share that there's

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a intense amount of work going on at the moment trying to come up with, much like we did for a definition of exacerbation, a definition of bronchiectasis to be clear about this and then to try to incorporate at some level what are we really calling COPD and bronchiectasis, bronchiectasis alone, asthma and bronchiectasis, because they phenotypically may in fact behave very differently from a natural history of disease course if somebody has COPD and bronchiectasis.

And so when we look at international groups from all over the world, what I call bronchiectasis in North America may be different than bronchiectasis in former Soviet Union or in Korea or Japan in this way to speak to your issue. But I don't know if we were to come up with a standardize definition that there's not similarities there.

And in fact -- and James can comment on this -- and one of the roles of looking at international registries, the Europeans, the U.S. and now the Japanese, the Australians, we'll be able to hopefully with an objective way do that exact work that you're asking for in a comparison study, are we really

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comparing apples with apples or is it really all the different balls, if you will, to help us identify that. But the issue that we wrestle with is, is a person that James sees in Scotland the same person that I'll see in Minnesota and I don't know that that's the case. James?

MR. CHALMERS: So I mean we now have some data because we have the European Registry which has over 15,000 patients enrolled including in the former Soviet states. And the Eastern European patients look nothing like the patients that we see in Western Europe and they look nothing -- so our patients look a lot like your patients, Tim; they're 60, 70-year-old females. They have usually idiopathic and post-infective bronchiectasis. They have a variable number of exacerbations and moderate lung function impairment. The patients in Eastern Europe are often in their 30s and 40s. They often have severe post-TB bronchiectasis, because that's the major etiology. They have very different spectra pathogens, but some of them very rarely exacerbate, which was what we saw in some of the clinical trials. So they have a completely

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different phenotype of disease. And so taking data from them and expecting to extrapolate that to the U.S. population I think is a stretch.

DR. AKSAMIT: Right. And even whether we're talking about post-tuberculosis or even smoking rate say between the two different groups and I think your data supports also even within Europe, Northern Europe to Southern Europe, I mean the phenotype and the microbiology has remarkable differences if I remember correctly.

MR. FOLLMANN: Yeah, so just a comment on co-primary endpoints. I don't see those, all those often and it seems usually they are a way of hedging your bets like you think, well, I don't know if I'll show success on total exacerbations of severity, so let's put them both in there. There's a cost to that typically where you have to, you know, use some alpha for each and so you increase the sample-size. So to me that's sort of a statistical consequence of thinking of it this way.

Another point I wanted to talk about, earlier we've seen -- you know, Susan mentioned the idea of

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total duration of exacerbations over the course of the year and then I learned, oh, the duration of exacerbation is just how long they get antibiotics, which is not very good really, but I wonder if there's some way we could try and hone in on like the severity of an exacerbation, maybe have an ordinal score something 1, 2, 3 or 4, so if you have two bad exacerbations that both get a score of 4, you get a score of 8 or something like that. Because I like the idea of the total burden somehow, but I see duration of exacerbations as measured by antibiotics is not the way to get out at -- maybe there's another way.

DR. ALLENDE: Yes. I want -- talking about the differences the -- in the epidemiology, I read also regarding this phenotypes that there's an association between the microbiology and the anatomical location whether they are bilateral or upper lobe bronchiectasis or lower lobe. And I wonder if that has been looked at in the differences between the different populations and the co-infections mainly. Dr. Chalmers maybe --

UNIDENTIFIED SPEAKER: James, you have a comment on that?

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DR. ALLENDE: James?

MR. CHALMERS: So the question was the differences in infection rates between lower and upper lobe bronchiectasis. Yeah --

DR. ALLENDE: Yeah, the association of the microbiology and the anatomical description whether they are bilateral, upper lobe, single lobe?

MR. CHALMERS: Yeah. So they really --

DR. ALLENDE: (inaudible).

MR. CHALMERS: They really don't predict microbiology or clinical phenotype at all. I mean, there are some patterns that you see, some middle lobe disease is more likely to be associated with NTM. Upper lobe disease you start to suspect things like Aspergillus disease or adult cystic fibrosis, but these are really rare issues compared to the general bronchiectasis population.

DR. ALLENDE: Could those co-infections play a role in -- with the -- and stratification be needed for --

MR. CHALMERS: So certainly NTM infection could affect things, but most of our trials have

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deliberately excluded patients with NTM infections up until this point. The concern I think for a lot of us is how well that testing for these other issues is done --

DR. ALLENDE: Exactly.

MR. CHALMERS: -- prior to enrollment in trials. I mean, I -- so we routinely test people for ABPA. We routinely send sputum for NTM, but I'm not sure that that's uniformly done everywhere and I'm certain -- I'm certain it's not done in some of the European countries. And so I think that is an issue. But the radiology itself is not going -- is not going to tease that out. You need --

DR. ALLENDE: No, but the association of --

MR. CHALMERS: Yeah. You need --

DR. ALLENDE: -- different etiologies --

MR. CHALMERS: You need to --

DR. ALLENDE: -- or co-infections.

MR. CHALMERS: You need the sites to test for those conditions.

DR. ALLENDE: Exactly. Thank you.

DR. AKSAMIT: And there would be the same

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experience in the U.S. registry as well.
DR. ALLENDE: Thank you. Yes.
DR. NICHOLS: If I could, I just want to revisit something James said a minute ago. So I was intrigued by the fact that it sounds like you saw a robust effect-size in the clinical outcome retrospectively of course, since the causality is hard there, but that's notable I think, and I just -- I'm curious if there's been an attempt to enrich your study population not so much based on exacerbation frequency, but rather the target of therapy, which is evidence of high bacterial burden in the airway and might that be something worth considering?
MR. CHALMERS: So I'm not aware that any study has done that, but if you just look roughly at the successful trials in bronchiectasis and the baseline bacterial loads, probably the most positive trial was the Gentamicin trial and the mean bacterial load at baseline was above 8 in that trial. The next possibly most positive trial was the colistin study, which narrowly missed its endpoint, the mean was around 8. And as you go down in mean bacterial load, you see

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lower success in those trials. So there is a -- there's some -- there's some reason to believe that targeting patients that have really quite substantial bacterial loads would be meaningful.
DR. NICHOLS: And is there a worldwide standard approach to quantify or semi-quantify? All right.
MR. CHALMERS: No.
DR. O'DONNELL: It's really only research -- research tool. All right. Have we any other comments? Yes, Jeff.
MR. ALDER: It's for -- question for -- I think it's implied if we're looking at a co-primary of total in severity, then there's doubt about whether total is itself clinically meaningful. That's why you might consider a co-primary. And if we're going to evaluate a daily chronic debilitating disease based on relatively infrequent acute events, then I would suggest not compounding the problem by making it a co-primary and trying to measure severity within total. And we tried to measure severity post hoc because in order to qualify patient had to have three -- at least

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three signs and symptoms plus the need for IV antibiotics. So within that questionnaire you could total up how many signs and symptoms?
Even post hoc we found it very, very difficult to come up with any meaningful measure of severity, duration. Duration varied by study center and what drugs they happen to prescribe and their prescribing practice. Hospitalizations varied by center and by country. And so I think the second half of question for in severity is going to be very, very difficult to put into place. Plus, it's also doubling down on the same endpoint, basically exacerbations.
DR. BARKER: If we're considering co-primary, I would at least consider having a biologic, and I use that in a broad term, in addition to a -- if exacerbation is one, there are emerging things and not FEV1, but elastase or other things that are emerging that give us some idea of both the pathophysiology as well combining it with the clinical.
DR. O'DONNELL: Any other comments on that? Any comments from our statistics colleagues here? Yes.
MR. ZIMMERMAN: What about just asking the

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patients how they feel?
UNIDENTIFIED SPEAKER: Yeah.
MR. ZIMMERMAN: I mean, it sounds really simple, but we're the ones that know. You guys can do all the lab tests you want and say, no, you're good, that's not always true.
UNIDENTIFIED SPEAKER: And the -- oh, sorry.
MR. CHALMERS: So actually the EQ-5 (ph) does that. It has five questions and it has just alliances just mark where you are. So there is some history of doing that. I do want to say something about getting frequent measures because this was attempted in the EI study, which was asking patients who were randomized to the continued monitoring to measure spirometry and I think they were just asked to do their symptoms score two or three times a week and that was a seven question scale and the missingness of data was rather large.
DR. O'DONNELL: From the audience side?
UNIDENTIFIED SPEAKER: Hi. Yeah. I had a quick question. So you know like in the asthma community how they have like the asthma control test. Would that be something like for the patients? It's

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only five questions and it says like how often has your disease kind of affected your work-life, your sleep quality and how do you feel overall it's being controlled? Could that be something you do even like weekly on like a app or something where you just track like five questions that kind of give a overall picture of your quality of life or is that like not feasible?

DR. O'DONNELL: I think that's where -- yeah, I agree, right, a simple, I think our friends in London have been working on a short sort of ACT type --

MR. CHALMERS: Exactly right. So there's a --

DR. O'DONNELL: Yeah, yeah.

MR. CHALMERS: -- there's a new tool called the Bronchiectasis Health Questionnaire, which is basically modeled on the asthma questionnaire --

DR. O'DONNELL: On the asthma questionnaire.

MR. CHALMERS: -- and the COPD CAT, which is very similar and it's five or six questions and it's how bad is your cough? How breathless are you? Have you had any exacerbations and it's exactly as you described.

MR. ZIMMERMAN: Is that a statistical --

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statistically validated thing? Can that be an endpoint, an outcome?

MR. CHALMERS: Yeah, so it's been validated within that population, so it's been tested in multiple centers. It correlates very well with other quality of life tools like the St. George's Respiratory Questionnaire. What it hasn't been is applied in a clinical trial to see if it changes, but it's a promising approach because it's simple and patients could do it more frequently.

MR. ALDER: I just want to plug a short daily diary would absolutely capture what we're looking for in severity. And that would be a built-in part by just asking the patient from some simplistic daily electronic diary. Patients that are spending two and a half to three hours a day on medication and I don't know why there's missing data, but something like this would take less than 5 minutes.

DR. O'DONNELL: Chris?

MR. KADOORIE: Yeah. I think a complication with some of these quality of life endpoints is the timeframe that it's actually measuring. You know, some

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of these, if you have -- if you're like intermittently looking at them at various days, they're not really capturing what you're really after which is the change from the baseline at randomization. So I think with these, if you're going to look at it every day, then you're going to have to -- you can't have any gaps. You have to, you know, be continuous -- it's continuous time-period linked to the baseline. And another thing I wanted to say is I think it's really important to rate the exacerbation and severity. I think that said, more work needs to be done in that area, that would be very important because, you know, frequency of exacerbations is a nice endpoint, but what if one treatment has very mild exacerbations and there's very severe.

So if you could somehow, you know, use the same kind of analysis with its total exacerbation because except for rate each single one and there you could use like a patient -- a patient opinion, patient reported outcome so you would have essentially similar to a frequency of exacerbations, but they would all be weighted according to how severe the patient thinks

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they are.

DR. O'DONNELL: Thanks. Sorry, do you have --

DR. SMITH: Sorry, was there another comment?

MS. HAMBLETT: I was just going to say, so we kind of skipped over three a little bit and I just keep going back to the one comment that, you know, even one exacerbation is important. So I think I was -- I'm sort of struggling in that if there is a therapy that reduces, you know, the proportion of patients, so reduces the risk of just one event, it seems that that may still be clinically important, and you know, whether that possibility still exists, you know, as an endpoint for a pivotal trial for, you know, a future company coming in. Obviously, you would hope, you know, that some of the phase II day that may form which endpoint, but my -- maybe either of those endpoints are meaningful.

UNIDENTIFIED SPEAKER: So, Nicole, can I push on that little bit? So if you have, as was I think pointed out a low incidence of events, but high impact of those events, from just a statistical standpoint, let's forget about just specific exacerbations,

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statistically how would you approach something that occurs very infrequently, but when it does occur it has a big impact to try to capture --

MS. HAMBLETT: Well, I think where it was kind of going, I was trying to step a -- get a few steps ahead in terms of the enrichment question. And if there are trials being done to enrich the population such that you're really, you know, boosting your probability of having event in your population that would become less of a problem is that maybe you would expect 60 percent of your placebo group to have an event if you get the right enrichment, you know, maybe that's a possibility. And that you could potentially, if you have that right enriched population then, be able to do a shorter study with time to first, as opposed to a longer study with rate.

And I'm just throwing that out there, you know, if it's still clinically meaningful. I think it's, you know, a question if you have -- if you actually need the multiple -- somehow, you're capturing severity with the frequency of exacerbations is that -- I think that's what you're kind of getting it, that you

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need the frequency endpoint to capture the severity.

DR. AKSAMIT: So let's, again just for argument sake, let's say you wanted to capture in the case of a cardiology study a MI every other year, every third year and then you were going to do an intervention trial, how would you set that trial up? If the expected events or MIs for once every other year, every third year and you wanted to have an impact on that, how would you set that trial up?

MS. HAMBLETT: Yeah, I mean that -- I mean that's a whole different --

DR. AKSAMIT: Well --

MS. HAMBLETT: -- discussion, yeah.

DR. AKSAMIT: Well, and that's different thing --

MS. HAMBLETT: Yeah.

DR. AKSAMIT: -- than the symptoms, so that --

MS. HAMBLETT: Yeah.

DR. AKSAMIT: -- I think if it's a matter of --

MS. HAMBLETT: Right.

DR. AKSAMIT: -- intervention with an

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antibiotic trial and trying to minimize antibiotics with an inhaled antibiotic is one thing, but if I, you know, kind of turn that around a little bit and say, well, let's look at nonpharmacologic interventions. So let's say something comes out to enhance airway clearance or something else, we might be able to then liberalize that and rather than using events only, start looking at other quality issues or other types of measures that we're not using antibiotics as the denominator for. But then again, in these other instances of having very low frequency as Jasan said that one event is too much, but it just doesn't occur often, but when it occurs it has a huge impact on us, quality of life and as most patients will share.

MS. HAMBLETT: Right.

MR. ZIMMERMAN: And the other thing to hardly compared to an MI, each of these exacerbations could very well kill us. And as much as I don't want to think about that, it's absolutely true. So that's why I don't want them to happen.

DR. O'DONNELL: What about number 3 since we alluded to that, the importance of the non time to

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first exacerbation or have we covered that sufficiently?

DR. SMITH: That or any other endpoint questions, because that gets into question 5 as well.

DR. O'DONNELL: Yeah.

DR. SMITH: So I mean any other comments about endpoints in general?

MR. HAWKINS: This is just out of curiosity, are there drugs that are on the market that were approved based solely on quality of life issues? Like we keep talking about quality of life questionnaires, but are they useful? Are they considered by the FDA to be valid and can they be made to be made valid?

DR. O'DONNELL: So the question is has the FDA used quality of life endpoint to approve the drug?

MR. HAWKINS: So not taking other factors into account, is it possible to make quality of life questionnaire that will be valid to the FDA?

MR. CHEN: Yeah, let me to try to answer that question. The quality of life is a very broad concept and then everybody interpret quality of life differently. It's ranging from symptoms ability to

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financing difficulty to emotional to social function, all that stuff. So in -- when you have a instrument that you broadly naming as quality of life, we actually look into what exactly that the questionnaire ask. So for example, in QOL-B is called the quality of life. It has social functions, emotional function, all that, but we concentrate on the symptoms of scale because that is actually more meaningful, more interpretable.

So I would say that the broader labeling quality of life is probably more difficult, more challenging, but we can actually labeling what exactly that instrument that is ask of the patient and what is actually interpretable and meaningful to the patients. So it could be like say relief of the symptoms ability, reduction of the days of exacerbations, things like that. Maybe when it is actually very significant large effect that we see say for example the daily activity, physical functions, that's also possible, but what -- if we put quality of life in the label, that is too broad, we need to be able to communicate clear to the patient what the drug is actually helping the patients, so not just the broad quality of life.

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MS. TRACY

: I think --

DR. O'DONNELL: Dr. Roach (ph) --

MS. TRACY

: I think the question was, if I can try to rephrase it, is, are there any currently FDA-approved products that were approved based on primary endpoint that was PRO-based using a validated measure?

MR. CHEN: Not in the non-CF bronchiectasis or CF, right, but this -- they are alert in other disease areas, other side would be the area that is actually the patient reporting is actually the primary endpoints. For example, in the female sexual dysfunctions that's, you know, basically that's the patient reporting their alert situation where -- and I may think this, in the psoriasis situation, the itchings, so that that you have to read that. So there are -- there are drugs that is basically the patient report is the primary endpoints.

DR. NICHOLS: Perhaps closely related would be inhaled aztreonam and CF played a major role in approval for that drug.

DR. ROACH: Hi, Jim Roach from Pulmatrix. If

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we could agree to a strategy on how to define severity of exacerbations, I could certainly see a role for perhaps a composite endpoint of total exacerbations frequency and severity because that might be a way to increase the power or decrease sample-size to hit what arguably would be clinically meaningful for both of those parameters. But I also heard that -- I think I heard that there was a concern that if you're only looking at frequency or time to, there could be a concern that you might decrease frequency, but miss more severe exacerbations. And I'm wondering if there's any precedent for that with pulmonary drugs, inhaled antibiotics or other drugs where you actually decreased frequency, but somehow you increase severity down the road. I'm just trying to think about biological plausibility of that.

DR. O'DONNELL: Yeah, I'm asking the CF colleagues. I know we heard that statement, but I'm not aware of any data to suggest that. Yes sir.

DR. DHAND: So one surrogate marker which might be -- capture some of this information that we've been trying to debate is the total amount of systemic

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antibiotics that we'll use during the period of the study because that might be able to quantify, you know, when -- what was the severity in the sense that the physicians thought that this patient requires 2 weeks or 4 weeks of antibiotics and that would also correlate with how frequently those occurred.

DR. O'DONNELL: Any comments on that using either antibiotic days I guess or antibiotic free days? I know that came up at the advisory committee --

DR. DHAND: From the total amount used actually.

UNIDENTIFIED SPEAKER: Yes.

DR. O'DONNELL: Yeah.

MR. CHALMERS: I would just -- I would just make a comment again from order and registry data is that the number of days of antibiotics patients receive is often a measure of who their physician is rather than the severity of their exacerbations. So 14 days is standard according to guidelines, but many patients in the U.K. receive 7, many patients receive 28. That's not a measure of how bad their exacerbation was, it's what their physicians' normal practices or which -

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- which physician they saw when they presented with their exacerbation. So again I think for an endpoint you would need something more objective that measures symptoms rather than drugs.

DR. AKSAMIT: Unless there was a standardized approach to the exacerbations; and as Dutch had pointed out earlier, you know, in the Cleveland area they use a lot of colistin and maybe other areas don't use it at all and that in itself will have a big impact on number of days of antibiotics. So it's not only the pathogen, but then the training unless there was a standardized response to exacerbations I think the noise is going to be too prohibitive.

DR. DHAND: Could that be protocolized though, you know, that -- no?

MS. HAMBLETT: I was just going to say, at least for many of our studies, the number of days of antibiotics has not been particularly sensitive. A few studies for which we've had quite remarkable reductions in exacerbation risk, but really no corresponding movement on the antibiotic days that you would expect to correlate with that. I think it's -- there -- it's

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very noisy.

MR. VANDEVANTER: I just wanted to comment on protocolizing exacerbation treatment, that's an excellent idea that will never be accomplished unless we get more data. What we find when we try to protocolize it is we either select for physicians that believe that's the right way to treat and then that reduces our numbers or we see a high number of protocol violations. And so many people think it's great in theory, but then when the patient is in front of them they go back to their training and those trials are problematic.

DR. O'DONNELL: Alan?

DR. BARKER: Just a comment on this frequency of exacerbations, as we get higher number of exacerbations, there are certainly patients that 2 weeks after their exacerbation they get worse or they get another course of antibiotics is that continuation of the same and how is that counted is the same one or is that a new one. And that would have to be defined if we're looking at a frequent exacerbation population.

MR. CHALMERS: Yeah. Again, the diaries could

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resolve that because if you see a return of symptoms to baseline and then an increase rather than a sustained high level of symptoms, you could make a better determination than just setting what we have at the moment, which is arbitrary thresholds of 14 days free cause a new exacerbation or otherwise.

UNIDENTIFIED SPEAKER: Yeah.

UNIDENTIFIED SPEAKER: Well, again like has been said, you have to be sure that your patients are every day a high number completing that daily questionnaire, which is a real problem.

DR. FROEHLICH: I have a quick comment on that. We in our protocol in the orbit studies, we defined that if a second cause of antibiotics was given within less than 14 days in between this would have counted as a single exacerbation. You can do this, but another episode explains or demonstrates how difficult this is in patients. I know at least of one case, probably more in our studies where a patient at the investigative side was diagnosed with a mild exacerbation and no antibiotic was prescribed. The patient left the hospital, a few hours later went to

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their personal physician and got his prescription of ciprofloxacin filled for the same event. And this is a difficulty that we are facing with many patients, some have standing prescriptions for antibiotics or they have their own perspective of what they need for treatment.

MR. CHEN: So I think these all come down to how we define exacerbations. And then I think we -- there is need for a consensus how we define exacerbation in these situations. The -- earlier we see there's a presentation that the actually symptoms of severity is included as the definitions that you need to have 4 hour the following symptoms, cough, mucus and all that. So if the symptoms severity is including in the definition of exacerbation, then actually that -- the days of exacerbation already taking into account on the severity of exacerbations. Earlier I mentioned about the use of PIO (ph), they actually do -- they want to capture the pre-exacerbations, you know, the up-tick of the symptoms.

And then they also major after the exacerbation, they actually capture how the symptoms go

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down. And actually, sometime you need to reestablish baselines because we also say 20 percent, they actually do not go down to baseline. So this has been -- consider has been study in COPD. I'm not so sure about in the -- in this patient population, but there are things that we can do. We just need to like, you know, have a agreement how to do it.

DR. FLUME: So in the CF forum we looked at the intervals between events to try and figure out when are they really two different events and when are they the same event. And if you've done adjudication, you've seen really short intervals. And when we started setting this up intuitively, we thought, well, a really short interval, maybe that's just a logistical thing. And then maybe if it's all within a week that actually represents they stop therapy too soon and it's just a worsening of that previous event and just sort of assume that maybe if it's more than 2 weeks maybe it will be a new event. When we ask doctors, it was always a new event.

DR. DHAND: You know, looking at symptoms also depends on not only the presence of the symptom, but

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the perception of the symptom as well. I mean, you could have a shortness of breath or cough or you know, sputum, but then is of new onset or is the patient been having that for a long time, how much does it interfere with their lives. And so I think that if you look at those factors to determine severity, that's going to be an issue as well. But included in your definition of the exacerbation is the fact that the physician changes treatment. So I think that -- you know, so that's the objective evaluation of those symptoms that the physician feels that a change in treatment is needed. So some of that I think would be a surrogate marker.

DR. O'DONNELL: Any other ideas for endpoints? James?

MR. CHALMERS: Just to throw something out there, when we asked the European Bronchiectasis Patient Organization (ph) what they thought was the most important endpoint, frequency of exacerbations was right up there, but the top one that bothered the patients the most was cough. And we don't currently measure cough in any bronchiectasis trial directly. So quality of life bronchiectasis questionnaire

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respiratory symptom score has some domains for cough, but is heavily weighted by other symptoms like breathlessness, and other. And so I just think it's unusual that we haven't yet found a way to measure what is the dominant symptom of bronchiectasis. Again, we couldn't advise company to measure cough using scale X because there isn't one validated for bronchiectasis, but there are ways of measuring coughs. So there's cough monitors they used in cough trials that are objective measures of cough, and there are questionnaires that measure the impact of cough, and it's something that should be considered because it's the main symptom the patients complain of.

DR. TINO: Anne?

DR. O'DONNEL: Yes?

DR. TINO: I agree with that and anecdotally our patients say the same thing. But actually, the question for the FDA -- the Leicester Cough questionnaire has been used in small clinical trials, one of the early Mannitol trials et cetera. What's your opinion about that as a measure or any of the panelists actually?

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DR. COX: I don't know that folks are familiar enough to be able to --

DR. O'DONNELL: Thank you.

DR. COX: -- comment right now on the questionnaire, but others may have thoughts.

DR. O'DONNELL: I guess we don't have good data on that. Yes, Igor (ph)?

UNIDENTIFIED SPEAKER: Yeah, I just want to make a comment. So when we went to the Pre-IND meeting with FDA many, many years ago, we had exactly the same kind of conversation about what is the right endpoint, all these clinical trials. And I think that the one thing that hasn't changed is that excess of patients always come up as an important endpoint. And I also remember at the previous workshop I went to Dr. Folly (ph) after the workshop when this was discussed and I ask him about, "Is he really, really sick, that a single drug would meet all of the concerns that the patients have about their disease?" So I think that, you know, the sponsor together with the input from the patients needs to decide what is it that they're going to demonstrate in the trial? I mean, if we had set out

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to develop (inaudible) of ciprofloxacin DI to suppress cough in the patients, we would have never been developing any ciprofloxacin for that purpose.

So I don't disagree that we shouldn't be monitoring cough. If we make these patients cough more that's a bad thing, but I think that in the end, we need to decide about what is the endpoint? And then if we meet that endpoint, put that endpoint on the label and then the patients need to decide whether there is an endpoint that they really like and this is why they would want to take that drug. I don't see that we can make a universal remedy for all the symptoms.

DR. O'DONNELL: I mean is there a way to make a composite endpoint between quality of life and frequency of exacerbations?

MS. TRACY: Certainly, I mean you can combine anything. However, I mean you need -- again that PRO has not been validated in this population. So going forward it would have to be tested in a phase II trial or a some sort of non-pivotal trial in order for that data to be collected to see whether or not that endpoint is validated and then put it into the

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composite I suppose. But I think your question is more statistical in nature, and, yes, much more complicated, and certainly analysis and you know, objectives.

MS. ELLENBERG: So if you had some validated way to grade severity, which we don't, apparently, but if there were a scale that people were comfortable with, one could imagine, you know, for each exacerbation having a grade of severity say for each day of the exacerbation, then one could do some kind of area under the curve, you know, over the period of time and add that up. But you know, that, you'd have to be able to validate that, that's just --

DR. AKSAMIT: I might push back a little bit on the severity issue as Dr. O'Donnell said when they adjudicated their severity for the purposes of the clinical trial what appeared to otherwise be a relatively simple concept became very difficult based on available information. The second part is that when the consensus statement came up with this international group about what a definition of exacerbation was as is pointed out in the discussion, the group purposefully left off grade of exacerbation, mild, moderate, severe,

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exactly for these practical issues.

So that in the context of defining exacerbations for clinical trials at least most of the -- well, the overwhelming consensus was leave the grading out, so it -- again it sounds great and I'm in full agreement with that, but in practicality based on the experience of Orbit (ph) and the other investigators, there was consensus not to do that. And I don't know if, James, again you want to comment?

DR. O'DONNELL: One last comment on this and then we'll talk about duration.

MR. CHALMERS: Yeah, no, I was just going to make the point -- I think Igor made a really important point and yours goes to the same thing that we mustn't make this too complicated and we mustn't create an endpoint that is so difficult to hit that we never get drugs through to patients

DR. O'DONNELL: That's where we are right now.

MR. CHALMERS: Total number of exacerbations is a really simple thing to measure and the other things that we're talking about like severity of exacerbations, the things where we don't have validated

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ways of measuring them are fantastic for secondary endpoints to provide supporting data of what this means for patients, but we really need to have an endpoint that we can hit and we can measure properly. And total number of exacerbations is the only one that we have that the clinical community has confidence in.

DR. SMITH: Okay. You know, that's a good point to take off on the question of the duration of the trials. And I think one reason that we're asking this is because based on what we've seen, if you're looking at a frequency endpoint it just seems that a 1-year trial may not be sufficient to detect differences between treatment groups. So that's partly behind -- now we understand if there were different endpoints, then, you know, the duration of the trial might be different. But we're interested to hear what people would say about the appropriate duration of endpoint.

DR. AKSAMIT: Well, and I might just put the caveat in, it depends on what the event rate is. So I mean as -- I mean in the context of your point which is very well taken in the experience with the respiter (ph) program, the event rate was exceedingly low based

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on what the expected events were going to be. And I can't speak to the CF trials, but if the event rate would have been four or five per year, would we have seen signal. And so I think we have to ask that question in the context of what do you expect the baseline event rate to be?

DR. SMITH: And it's true, we're going into these trials, the expectation was that the event rates were going to be somewhat higher than they turned out to be. So it's pretty, you know --

DR. TINO: So you know, the duration is going to be a very important question because there's been an impact on some of the guidance that FDA has given in terms -- even at the upcoming colistin trial. So from an academic standpoint, I think the longer the better in terms of a disease where we've seen that the event rate can be relatively low. But from a practical standpoint in the placebo-controlled trial in a group of patients who has the kind of morbidity that suffered, it can be very, very impractical to do that. The off-label use of these inhaled antibiotics is going to continue. The doc in the office is going to use

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tobramycin, is going to use colistin. So I think -- and I think we should certainly hear from the patients who alluded to it. I think ideally it would make sense, but from a practical perspective, I think 2 years is too long and I don't think we're going to complete clinical trials to our satisfaction.

MR. FOLLMANN: I was just going to make a pretty obvious comment which is, you know, the duration -- the feasibility of a trial is related to how many people we recruit, and you know, it's basically based on how many events you get. If you need a hundred events, you could recruit a lot of people who have very -- events very rarely or you can recruit very few people who have a lot of events. And so it's all tied up together, duration by itself in my mind it's not -- is incomplete I guess.

DR. FROEHLICH: The experience with a tool phase III Orbit trials in my mind is -- confirms if you have a sufficiently high event rate in particular in the placebo group, you will -- you do see a difference in the frequency of exacerbations when you use it by nominal method, and when we were to use the counting

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process we did use the NSM guild (ph) counting method as a post-hoc analysis. You narrow down your confidence interval and you get even better results. When you look for the Orbit-3 (ph) study that has a much lower -- not much, but has -- had a lower rate as compared to Orbit-4 (ph). There you did not see a significantly positive result for the frequency. And I think in my mind it really comes down in the identification of those patients that have a higher disease severity in terms of a higher frequency of excessive patients in your study.

MR. FOLLMANN: Well, where there are fewer events in Orbit-4 maybe if Orbit-4 enrolled more people that could have counterbalanced them not having many endpoints. And you'd have similar total events in 3 and 4 and maybe showed 4 was significant.

MR. ALDER: There was no big difference in the enrollment rate of 4 studies, but there was a difference when you looked at the placebo, event rates was -- in our interpretation Orbit-4 was unusually low.

MR. FOLLMANN: Right, so you had fewer events in Orbit-4 which could have, you know, if you had a

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bigger study you would have had more events. So you could have, you know, made Orbit-4 bigger. I know you didn't plan on that. I guess they were identical studies and for bad luck, you had fewer events in Orbit-4. But to me it's not just a question of, you know, you can counterbalance usually having few events by enrolling more people and getting more events, power is basically given by a number of events.

MR. ALDER: Sure, we did base our studies on phase II results and in one study we were closer to the phase II results, in the other one we were not.

DR. TINO: Again, I'll say, the respiter 1 and 2 were enrolled based on total events, not event rate. And in the first respiter trial, the placebo event rate per patient, where there was significant efficacy was about 1.1, and every patient had to have a history of 2 or more. In the second respiter trial where it just missed on statistical significance, the event rate in placebo is 0.7. So you know about -- what is that, about 28 percent lower. So there was better efficacy when there was a higher event rate, but both trials were still enrolled the total number of events. So

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there were more patients in the second trial than the first because of the lower event rate overall. It didn't help in other words. You still need a high event rate per placebo patient.

DR. SMITH: I just want to comment on a challenge with extending trial durations in that there's an unintended consequence there that the longer the trial is, the more likely you are to recruit relatively healthier patients. And so you may think that we have this event rate for a year trial, so if we extend it to 2, we can extrapolate it out. But I think what you would find is that you would lose more signal than you would -- more signal per unit time than you would gain by doubling the time.

And honestly a year is a long time for these patients to be in these placebo-controlled trials. And so at least this has been our experience in CF is that the longer the study you propose, the more likely you are to recruit patients that have a lower medical need.

DR. AKSAMIT: And I think one difficulty is based on what we've seen so far would be hugely risky for somebody to undertake a trial looking at frequency

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and have that trial be one year because it may well fail. Unless you've got a way to identify which we haven't quite seen yet, the really frequent exacerbaters.

DR. SMITH: Yeah, I'm not denying that that risk is there, but what I'm saying is extending the duration is not necessarily going to mitigate that risk.

DR. AKSAMIT: And I think the experience with the respiter program that there was significant geographic variations between the respider-1 or respider-2. On the other hand, it was more difficult. I think most of us that had enrolled patients in rolling in a respider-2 and as a consequence of that, it speaks to these issues that the more -- the larger the population the longer it goes, the much more difficult time we're going to have enrolling patients anywhere here or internationally and so we have to be mindful of that.

UNIDENTIFIED SPEAKER: I just want to ask the question, is there a way of doing this, you know, instead of doing a 2-year or longer study, is there a

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way of doing a shorter, you know, I think it was 48 weeks for one of the studies or a year. And if everything sort of looks okay, so there's no, you know, safety concerns per se, is there a way of doing a tentative approval where patients would continue on the drug, maybe not do the placebo, continue on the drug and then be able to analyze?

DR. COX: So I mean the question comes up every now and then about tentative approvals, and in essence in order to approve a drug, I mean you do need to have both the evidence of safety and efficacy. So it's an interesting idea, it comes up from time to time, but we really do need to have the data that would support the approval to allow us to go forward. So you know --

MR. CHALMERS: Just a comment about enriching for higher numbers of events, I mean, so in the COPD literature, the major application of the exact PRO diary that you mentioned earlier has been to actually trigger physicians to diagnose events. So in COPD trials now it's very common that patients will use the diaries not as an endpoint, but it will alarm in the

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physician's office to say your patient is having -- has had 2 days of worsening symptoms and you contact the patient and the patient says, "Yes, I'm having an exacerbation. Sorry I forgot to contact you." And at the moment in trials, we rely on then seeing that patient 3 months later and then reporting to us that they did have an exacerbation that they forgot to tell us about.

But if we have the objective measure, the triggers, the reporting of exacerbations, it's proven in COPD that in some cases it doubles the event rate just by detecting unreported events. So it's like another thing that's important to think about.

MR. CHEN: I'm thinking of another scenario is that instead of the total as the patient or the frequencies, say if the treatment objective or the treatment benefit is actually decrease the days of the exacerbations, reducing the durations. In this case we can actually when patients come into the hospital or the emergency care to the clinic reporting that they are having exacerbations, then we're enrolling into a study and then to -- then we randomize them into

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different arms and then to see if the target treatment actually reduced the number of days after the exacerbation, in that case you don't need the -- a very longer trial, but then your indication will be different, will be rather than total among, or total number of exacerbation, but is actually the number of days of experience as the patients.

DR. BARKER: The comment about the practical utility of 2 years is come up, the longest study we've ever done is a year. But there's both patient and investigator fatigue, you're talking a minimum of 10 to 12 visits per year as part of the study. You're talking about ideally coming in for their exacerbations to be evaluated and that's -- it's fatigue.

MR. ALDER: Or data fatigue. Yeah, I'll say with longer trials there will be diminishing return in that even with a 1-year study. When it's placebo-controlled, there's market numbers, the dropouts. And the dropouts tend to happen during or after an exacerbation. Now statistically there's ways to compensate, but that's less than ideal to have patients dropping out, especially if the patients know there's a

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50-50 chance of being in the placebo arm and naturally they perceive that they're not receiving benefit from being in the trial, therefore drop out. So going to a 2-year trial, I would expect we will see even more dropout rate and less and less data coming in.

MR. CHALMERS: It's important that we recognize that guidelines now in Europe, in Australia, New Zealand, in Spain, in all of these countries recommend inhaled antibiotics for people with pseudomonas and frequent exacerbations. So the conversation you're having with the patient now when you enroll them into one of these trials is, "I could give you an off-label antibiotic now because that's what the guidelines say. But I want you to do this trial because it's good for your fellow patients to demonstrate the effectiveness of these drugs." And the patients are extraordinary because many of them will say, "Yes, I will take the risk of having a placebo in order for the greater good rather than taking the off-label therapy that's available now." But that conversation gets even more difficult when it comes to a 2-year trial, and I don't believe any of my patients

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are going to agree to do a 2-year study where they can't take off-label therapies. It's just -- it's ethically very difficult with what the guidelines currently say and the patients are already making a huge sacrifice to do 12-month studies.

DR. O'DONNELL: All right, with that any last comments from the panel or the audience? Great, thank you very much.

CLOSING REMARKS

DR. COX: So I just want to thank everybody for the discussion today. I found it very informative. It was very helpful to hear, you know, what we've learned from past trials, both the things that have worked and the things that still need more work in essence, you know, some of the gaps that still need to be solved, some of the questions that still need to be answered, to try and get to trials that will be informative and ideally more feasible so that, you know, effective therapies can be found to be able to treat patients. I also want to thank too the patients who contributed their, you know, comments and thoughts about endpoints and helped us to understand more about

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the disease condition. I greatly appreciate it, and also the speakers at the public comment period.

So I think it's been a good day and I think this, you know, the discussions today will help us in discussions with companies that are interested in developing therapies in this area, and should help us to move forward. We greatly appreciate everyone's willingness to come and join us here today and we realize that you're all very busy and this takes a big chunk of time out of your schedules to travel in and travel out, come join us. But we really do benefit from it tremendously, so we're very grateful for your willingness to come and do this. It's very valuable to us and I'll pass the microphone to Sumathi.

DR. NAMBIAR: Yeah, I just want to add my thanks as well on behalf of the division. Really appreciate all of you coming and sharing your thoughts and ideas, and I think you've given us some food for thought, and hopefully this would be helpful as we forward. And many thanks Chip, Jasan and Mary (ph) for participating. We really appreciate it, thank you.

DR. COX: Great. So safe travels home

everybody, but one more announcement from Anne.

DR. O'DONNEL: One last comment, the World Bronchiectasis Conference is here in a couple weeks here in D.C., so if anybody wants any further information --

UNIDENTIFIED SPEAKER: Information, yeah.

DR. O'DONNEL: -- let us know. Thank you.

DR. COX: Great. Thank you all.

(Applause.)

(Whereupon, the meeting was concluded at 4:22 p.m.)

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July 10, 2018

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