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PARTICIPANTS:

SESSION 4: Clinical Use of Bacteriophage Therapeutics:

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Early Clinical Experience with Phage Therapy:

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Clinical Development of Bacteriophage Therapy Products:

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An Overview of Adaptive Clinical Trial Design:

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Phage Susceptibility Testing in Support of Phage Clinical Trials:

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Phase 1b Experience with LBP-EC01, a CRISPR-Cas3 Engineered Bacteriophage Cocktail Targeting *E. coli*:

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Addressing Emerging Antimicrobial Resistance with an Adaptive Library of Bacteriophage--PhageBank:

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Adaptive Phage Therapeutics

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P R O C E E D I N G S

(10:00 a.m.)

DR. SCHOOLEY: Good morning, everyone. I'm Robert Schooley from the University of California San Diego, and I'd like to welcome you to day two of the joint NIAID/FDA symposium on bacteriophage therapeutics.

Today we're going shift gears and spend some time talking about clinical experience and clinical development. I'm very delighted to have—to start out with someone who's had a lot of experience with phage therapeutics, Dr. Saima Aslam from the University of California San Diego, who will talk about early clinical experience with phage therapy. Saima.

DR. ASLAM: Thank you very much. I'm hoping you all can see my screen? Okay. I think that's a yes. Okay. So, first of all, good morning everyone, and thank you Jane and all the other organizers for inviting me to talk to you and share my experience. I think I'm on a video. Okay, sorry.

So, conflicts of interest are noted here and—okay. I wanted to start off by acknowledging the efforts of many people whose work is reflected in the cases that I will share with you all today.

I wanted to start, really, just giving an overview of the work that we've done at IPATH. As you know, Tom Patterson was treated in 2016, and it took a couple years with efforts from Stephanie and Chip to develop IPATH in 2018. Over the past three years, we've fielded over a thousand requests—consults for phage therapy across the world. The majority of these, we thought that phage was not indicated for a variety of different reasons. We did eventually recommend phage hunts in about a 190 of them. And as you can see only a small percentage, so, 28 people have been treated to date and 11 have phage therapy pending.

But, you know, even among the people in whom a phage hunt was recommended, phage were found in about 77 of them. And you can see sort of reasons, you know, why there was,

you know, loss of people really from finding phage hunts to actually treating patients. And for some, the treatment came too late. For some, the infection had resolved. And you can see a few other issues listed there as well.

So, the top two organisms for consult that we had were *Pseudomonas,* which is our number one, followed by *Staph aureus* and *M. abscessus*. So, and I think this is reflected in data that Dr. Fiore shared yesterday as well, mirroring the INDs that they see at the FDA.

So, UCSD, so far, we've treated 13 patients, and I've listed them here. And you can see that we have a variety of different, sort of, infections and organisms that we've treated. Most of them are *Pseudomonas*. About half of these cases are patients who have MDR *Pseudomonas* infections. We have some with *Staph aureus*, ESBL *E. coli*, as well as *Acinetobacter baumannii*.

And then, we've treated a variety of different infections as well. So, this includes device-associated infections. So,

LVAD and prosthetic joints, recurring bacteremia, recurrent UTIs, and then pneumonias in the setting of lung transplant, as well as cystic fibrosis. And you can see our outcomes listed here as well.

So, when we talk about clinical phage therapy, in my mind, there's two main questions that I think we need to answer. The first is, is it safe? And the second is, does it actually work?

So, in terms of safety, at least at UCSD, when we treat patients with phage therapy, we have a pretty comprehensive monitoring plan for them. So, this includes checking vital signs, you know, both during treatments but also around the clock. When patients receive their first dose of phage, we have an anaphylactic kit at bedside in case there is an anaphylactic or other reaction, we can take care of it. And so, that first dose is usually either in a clinic setting or an inpatient hospital setting where patients can be closely monitored.

For all our patients, we also had to

take blood work minimally at a weekly basis. So, this includes checking liver and kidney function, blood counts, in particular white cells, hemoglobin, and platelets, and then inflammatory markers as well. And patients keep a detailed symptom diary, and then we see them clinic once a week for outpatients, which has been actually about half, well, more than half our cases. And if they're admitted to the hospital, we see them daily.

And this is an example of a patient diary that they're given. So, this is a daily diary with doses and the kind of symptoms that they've had. So, when they come in every week, they bring their weekly, you know, diaries or entries with them.

So, in terms of the experience we've had here, you know, 12 of our patients received IV therapy and two patients received two courses, so that’s 14 courses of IV phage therapy. And of these, one patient did have a serious adverse event. Two patients received nebulized phage therapy and neither had an adverse event related to that.

We did not see any change in kidney or liver function over time and we did not change—see changes in CBCs, other than, you know, elevated white counts at the beginning of an infection that either come down or resolve with treatment. We did not see development of anemia or thrombocytopenia with IV phage therapy, or actually, IV or nebulized phage therapy.

So, in terms of the main serious adverse event we had, this was a patient with an LVAD that developed shortness of breath, wheezing, chills and fever within two hours of a new phage formulation that he received. And these symptoms actually recurred at the next consecutive dose that he had, at which time we then stopped phage. He was treated with antipyretics, antihistamines, inhaled albuterol, as well as IV steroids, and his symptoms resolved.

And we subsequently restarted the same phage formulation three days later. But this time we went with a dose escalation study in which we started off with, you know, highly

diluted dose and then built up, and the patient tolerated that well. And we continued that at a dose that was one log less than where we had started which was 10 to the eleventh, was his initial dose.

And so, he tolerated it well, which makes me think it probably was not related to the phage itself. Potentially it could have been related to either dilutants, that were in the actual phage solution that then diluted down, once we, you know, reduced or made dilutions of the phage itself.

The other thing I wanted to point out, you know, with two patients, both of which had *Pseudomonas aeruginosa* LVAD infections. Both of these patients developed bacteremia within one week of IV phage initiation. Both of these patients actually had negative blood cultures at time zero and this occurred, you know, for one patient it was three days later. For another patient about a week later. Both of these patients developed, or actually cleared the bacteremia with a change in antibiotics as the organisms

had different antimicrobial susceptibility patterns then where we started with. And then, for the organisms that occurred in these breakthrough bacteremias, we noted that they retained *in vitro* phage susceptibility to the phage that was being used and we continued using it.

So, this is just a timeline of one of these patients. This was one of the *Pseudomonas* LVAD patients whose driveline is depicted here in the picture. He received six weeks of phage therapy, and the blue arrow in the beginning notes a negative blood culture. And then, the red arrows are positive blood cultures for *Pseudomonas*. And these eventually cleared as we changed antibiotics and then did not recur. The isolates that are circled, as well as the one that we started off with at baseline, were all sequenced. And by sequencing, at least, they all seemed very similar.

So, when we talk about does phage work? You know, so far, at least from our side, we have, you know, a number of case

series that I think the success, or successful case series are reflected from many other publications, you know, within the U.S. as well as around the world.

For the patients that we treated successfully, you know, these were seven patients. Again, they had a variety of infections and I think the key point is that all these patients actually had, you know, failed multiple rounds of antibiotics and other therapeutics in the past. And so, you know, were truly antibiotic recalcitrant infections and were then treated with a combination of phage as well as antibiotics. And so, I think seeing these seven successes, knowing that all these patients had failed multiple times before, it's pretty impressive. But certainly, we had failures as well.

So, I don't have time to really go over these in detail and so, what I wanted to do was, basically, go through some observations that I think are pertinent as we discuss clinical trials today.

So, one was that targeted phage

therapy can be a microbiome-sparing approach to treatment. And so, this is a patient that had a *Staph aureus* LVAD infection. And, as you can see in the picture, it was pretty severe, and this patient actually had multiple rounds of bacteremia and osteomyelitis and surgeries. And a couple years later when I saw him in clinic, he basically had, you know, an open, gaping chest wound in which you could see his device.

So, he was treated with four weeks of IV phage therapy that were added on to his cefazolin and minocycline. He tolerated treatment well with no adverse events and, at the end of treatment, at four weeks, he had negative sternal wound cultures. And so, what I show here in the figure are basically skin swabs over time, in which we show that were was a significant reduction in the log ratio of *Staph* to *Corynebacterium* in the skin. So, if you're pointing again towards the targeted nature of phage therapy, as well as that effect remains. So, the blue lines that you see, or the blue dots, are related to

post-phage therapy effect.

Additionally, the patient had serial swabs from his saliva and stool over time and we noted that there was minimal variance in his, in the gut microbiome during the time he received phage therapy. Showing again that there was minimal damage to his gut when we added on targeted phage.

The other thing that we hear a lot about is immune response, and these are three separate patients. And they developed an immune response to phage. All of these patients were treated successfully and so, I'm not, you know, clear on how, what that effect is on outcome.

So, the first case, patient is the one I showed earlier with the *Staph aureus* LVAD infection. Over four weeks of phage therapy, he developed serum neutralization which was, when we look at that K- value, in general, was low. So, anything less than 10 is considered low. So, he did not really mount a, you know, an aggressive immune response to phage and was successfully treated.

The patient here is someone who had an ESBL *E. coli* UTI that was treated with two weeks of phage therapy, as well as IV ertapenem. And in this patient, we can see by week two of phage therapy, there was complete serum neutralization that occurred with phage therapy. But again, this patient had a successful clinical outcome.

The last patient is one of the *Staph aureus* prosthetic joint infection. This patient had previously failed a course of *Staph aureus* phage and so, we treated her a second time. And when we treated her that second time, we collected serum samples both at initiation as well as over time. And so, even pretreatment, which is the orange bar, at pretreatment, you know, one hour of incubation, you can see that there was complete serum neutralization. And, at the end of treatment, you know, six weeks later, there's also complete serum neutralizations that occurred, you know, immediately at time zero.

And so, again, you know, this

patient was successfully treated despite even having preexisting serum neutralization. So, I think, you know, it's unclear what that means in this case. I think something that we need to study systematically.

The other thing, and this is from the Tom Patterson case, the phage/antibiotic synergy can also be harnessed for clinical success. In this case, patient had an MDR *Acinetobacter baumannii* with very, you know, minimal antibiotic options. So, when phage and minocycline were combined, we saw a synergistic effect which is that turquoise line that you see.

And some of this, I think, is very specific to, you know, the bacteriophage combination as well as the antibiotic combination. And again, something that we should check, you know, when we treat each patient to see if there is a synergistic combination that exists or not.

We can also use a change in bacteria susceptibility using phage and that may lead to clinical success in treatment. And this was

a lung transplant patient that had a highly drug-resistant *Pseudomonas* infection at baseline. But with phage therapy, we ended up with isolates that were much more amenable to antibiotics. And this we've seen, actually, in several patients but this is an example of one of them.

Additionally, I think phage can also be used in the setting of antibiotic toxicity. And this is a young 24-year-old female who had respiratory failure in the setting of CF and a highly drug-resistant *Pseudomonas*. She received IV phage therapy, clinically improved. Before she was on phage, she was on colistin as that was the only drug, you know, we could use on her and had renal failure. And so, once we started phage therapy, we actually stopped the colistin and that led to the resolution of her renal failure, in addition, you know, to treatment of the infection that we wanted to treat. And she underwent successful lung transplantation nine months later.

And also, I think of note is that

once we treated this, she had no further recurrence of a CF flare for about three months. Previously, she had flares, you know, almost on a monthly basis. This also allowed her rate of recovery time prior to transplant.

So, this is another patient in which we think the clinical success was achieved by bacterial succession. So, this is a patient that had recurring ESBL *E. coli* UTIs, in a setting of a transplant. The patient received four weeks, sorry, six, two weeks of IV phage therapy and then six weeks of concomitant ertapenem as well.

When we used phage, one, again, there was no adverse event in this patient. We saw clinical resolution of the infection and then, I think the key event here was that patient has no recurrence of further UTIs with three months of follow up. And, in this case, previously the patient had reoccurrences every two to three weeks. So, clinically it worked.

After treatment was stopped at week eight, we noted that the patient did have a positive urine culture with *E. coli* but was

asymptomatic and did not require antibiotics. And this *E. coli* remained susceptible to the phage that we had used, with similar MOIs. The team at Baylor did genetic sequencing of both the original strain and the second strain that we recovered following treatment, and they noted a variety of SNPs, insertions, and deletions between the two that included areas that pertained to bacterial attachment, motility, and potentially other virulence elements.

And so, again, I think that's something that we need to study and, you know, kind of consider as a potential therapeutic option in treatment, in clinical trials.

So, I showed you a number of cases that were successful and, you know, the true test of any drug or therapeutic option are clinical trials. And so, so far, I think those unfortunately have been disappointing. And so, these are results on the PhagoBurn trial in which underlying, in which, you know, standard of care, silver sulfadiazine, actually was better than topical *Pseudomonas* phage that was

applied to infected burn wounds.

This is a study in which saline rinses of *Staph aureus* were used, *Staph aureus* phage were used, for patients that had chronic rhinosinusitis. In this study, you know, it was safe and tolerable, but only two of the nine patients actually had microbiological eradication of the *Staph*. And five of nine patients had ongoing symptoms and actually needed treatment following end of phage therapy.

And then, most recently, is the study looking at the use of intravesical bacteriophages for treating UTIs in patients undergoing prostate surgery. And so, this was a randomized, placebo-controlled trial. And again, in this study, the main outcome was treatment success, which was related to a sterile urine culture, and in this study, antibiotics were better than phage, you know, numerically, not significantly or statistically in this study.

When they did a post-hoc analysis just looking at reduction in CFU of bacteria

in the urine, they noted that antibiotics, you know, led to a statistical reduction. The use of phage did not. Again, adverse events were very similar across the groups.

So, I think, you know, these clinical trials, unfortunately, you know, were disappointing, but I think they're helpful in terms of learning from them, and hopefully, you know, design better clinical trials. I think one of the main issues, at least in the PhagoBurn trial, was stability of the product. And their phage titers had actually decreased by three logs within two weeks following manufacture.

Also, the amount or concentration that was actually used at treatment was minimal, so, very little in PhagoBurn. And then also, in the bladder, in the UTI study, patients received bladder irrigation and that probably just diluted the phage that was being given intravesically.

In the PhagoBurn study, the cases that were treated successfully, were based, were associated with baseline susceptibility

to phage. Which, I think will be, is an important study criteria as we move forward in clinical studies.

And I think it also, sort of, highlights, you know, how best do we give phage therapy? So, in that PhagoBurn study, phages were applied by an alginate dressing which probably led to some adsorption of phage and also led to reduced active phage at site of infection.

And then, the intravesical ones also, were probably just washed out once, you know, with bladder irrigation.

So, I think that highlights issues in trial design as well as study outcomes that I think will be discussed later today. Some of the reasons, you know, that led to failure of these studies, I think probably are common across the board as I think of studies in general. But then some also may be specific to the kind of infection we're treating or the, you know, specific bacteria/phage interactions as well.

So, we have a number of limitations,

you know, just with clinical use, whether it's for a case patient, case report-type patient or a clinical trial. But I think stability of phage is a really important issue. You know, what temperature do we keep it at? How long is it stable for? How we package it, etc.

Currently, for our patients that have received phage at UCSD, in general, it's been a pretty convoluted process that's involved compounding at the research pharmacy level. And also, complicated for patient self-administration though, you know, doable. Manufacturing, I think, will lead to some of these, or hopefully resolve some of these issues.

There's also a delay from when we actually, you know, recognize that a patient may benefit, from then getting ordered isolates to doing susceptibility testing, to then actually finding and treating the patient. And this may be from weeks to months. And you saw, initially, that some of our patients actually, you know, had passed away prior to actually getting phage.

I didn't really go over resistance in our patients. This is something that was discussed a lot last, yesterday. But certainly, I think this is an important goal, potentially for synergy as well as phage engineering to overcome this.

And then, again, I think immune response is unclear. Certainly, you know, there's a publication of Dr. Hatfull's group recently, in which failure of therapy was associated with an immune response. But we haven't seen that in our patients.

And so, the other things I think we need to think about is—and this is with the two pseudomonas LVAD patients I discussed—that we need to think carefully about which, who is a, you know, a good patient or a certain patient population that we treat since we do not want to cause, you know, any harm by allowing other MDR pathogens to grow in there at niche.

So, from a patient perspective, I think it's important, you know, as we develop trials, you know, what goals are important for

patients? So, one, obviously, is safety that I think we all agree on. For most patients that I've treated at home, I think the practicality of it hopefully makes it more widespread use. I think the definition of success, at least for compassionate use cases, is something that should be discussed clearly with patients and to be agreed upon at the outset.

I mean, we all want a cure of infection. Sometimes that cure, you know, or sterile culture may not be achievable but what are additional desirable outcomes? And so, some of these include just, you know, improved quality of life, I think not requiring IV antibiotics anymore, being out of the hospital because, you know, they're not sick enough to be in time.

For recurrent UTIs or other recurrent infections, perhaps just an increased time to recurrence I think would be helpful.

In the setting of lung infections, looking at FEV1s, which gives you an idea of how well that lung is functioning also, I

think, is helpful in terms of an outcome.

So, I'm going to stop here and summarize with this slide. I love the slide, it's from Dr. Jean-Paul Pirnay. Mainly because I think it really highlights the desperation that we feel on the clinical side in terms of the need for new and effective treatments for so many different infections. And also, you know, the success that we've see in the phages and our interest in using them, which is reflected in these increasing amount of INDs and, you know, phage therapy consult requests, the compassion-use cases.

And I'd like to, kind of, counter that with this, you know, logical response of Spock. You know, our faith, I think all of us are believers, which is why we're here. And I think we really need to work harder in really developing the proof that it is truly, you know, a future therapeutic option.

So, I'll stop here and hopefully we can talk some more in the discussion section. Thank you.

DR. SCHOOLEY: Thanks very much, Dr.

Aslam. We get to questions and answers during our open panel discussion later this morning.

We're now going to turn to clinical development of bacteriophage therapy products from Dr. Rebecca Reindel from CBER. Dr. Reindel?

DR. REINDEL: Good morning. Can you see my slides, Dr. Schooley?

DR. SCHOOLEY: We can. You are on the non-presenter mode though, if you could just switch to presenter mode, it should be good.

DR. REINDEL: All right. Sorry. There it is, sorry. It was hidden. There we go. Is that better?

DR. SCHOOLEY: Perfect.

DR. REINDEL: All right. Apologies, it was hidden in my display. So, my name is Rebecca Reindel. I'm a medical officer in CBER, in the Office of Vaccines Research and Review. And Dr. Aslam has provided me with the perfect segue into, you know, how do we provide that proof that Dr. Spock so desperately needs? And I'm going to talk about the clinical development of bacteriophage

therapy products.

So, the disclaimer is that my comments are an informal communication. They represent my own best judgement, and any information that I present or discuss today does not bind or obligate the FDA.

So, some general principles when we talk about clinical development of bacteriophage products. These are biological products that are regulated in CBER, in our office, OVRR. They're considered drugs when they're used to treat, prevent, cure, or mitigate a disease in humans. And the clinical use of unlicensed bacteriophage products in the United States must be conducted under an IND or an Investigational New Drug. And that's in our regulations, the Code of Federal Regulations, 21 CFR 312. And this has been covered extensively in other FDA presentations, but the FDA licensure of bacteriophage products will require that we demonstrate that they are safe, pure, potent—meaning effective—and that they can be manufactured consistently.

So, I have 20 minutes to tell you all exactly how to conduct clinical development of bacteriophage, which is obviously an inadequate time to go through everything. So, I'm going to go through some things briefly here and then we have breakout sessions later. And at that breakout session, I'm going to talk a little bit more in detail about some of the information on the slides here, in terms of clinical trial design considerations.

And we have a great talk following me about other aspects of clinical trial design that will be very helpful in that regard. So, I'll gloss over those slides at this time, but know that I'm willing to discuss those in the breakout session. I'm also going to talk about some other programs that are available through FDA and information on patient experience data.

So, how can you engage FDA throughout development? And there are a number of formal meetings. You can see on the bottom of this slide, there's the map icon and then,

the link to a specific guidance for industry that's relevant for that given slide. So, when you're looking at these slides later and you want to have a quick and handy way to access a relevant guidance, it's there. And these guidances, if you don't have experience using them, they're very helpful. So, there is going to be a separate breakout session specifically on FDA meetings. So, if you choose to attend that, again, you can get a lot more information here.

But just briefly, the most common type of meeting that we have at FDA are Type B meetings. These can include pre-IND meetings, pre-BLA meetings, and the Phase 1, 2 or 3 meetings. And these are, sort of, the most common meetings. Type A meetings are necessary for product development that's stalled, or Type C meetings is really anything other than a Type A or Type B meeting.

So, we really encourage you to request a pre-IND meeting with us. To optimize the value of your meeting, the meeting packet should provide all the summary information

that we need that's relevant to your product, any supplementary information, so that we can answer any questions you have and provide as helpful feedback as possible. So, it's really critical that the entire meeting package contents support your intended meeting objective so you can get the most out of the meeting.

And again, consult the relevant guidances, and there are guidance documents. In order to help you put together what you'll need for an IND, you can go to the FDA website and look under guidances for drugs and then search under investigational, and you can pull up a number of relevant guidances.

What can we talk about in our pre-IND meeting? CMC issues, any questions you have about nonclinical study design or the results you've obtained thus far and how that might inform your clinical study design. We can look at, you know, proposed clinical study designs and clinical protocol components and provide feedback for you. As well, we can answer any questions you have about regulatory

concerns.

So, we're required at FDA by law to provide some version of this slide. Just kidding. But you'll see that this slide matches a lot of the slides that have been presented by FDA staff. And really, it talks about, you know, the timeline for clinical development. And I've added here some relevant time points where you can engage the FDA.

So, during your preclinical development, before you go into humans, you can have a pre-IND meeting with us. And as you progress through your clinical development, looking at safety, dose, expiration, and preliminary effectiveness in your early phase studies, and then progressing to more pivotal or registrational studies in Phase 3, where you're looking more at effectiveness and safety, you can have several meetings, including the End of Phase 2 meeting, where you can get input on how to, on your proposed Phase 3 studies, as well as a pre-BLA meeting when you're, when you feel like you have sufficient data support a BLA.

So, I just wanted to talk for minute about indications. So, I have a picture of the sun here to remind everybody that your indication is the sun around which your clinical development program will orbit. So, really, when you start thinking about your clinical development program, you want to be considering the indication and usage—meaning who's going to be getting it, what population, what will they have, what's the disease you're going to treat—and you want to be thinking about that really early in development.

So, who's going to get treated? What's the disease you're going to treat, prevent, or mitigate? Is it going to be anatomic location, disease process, a specific bacterial species, a specific resistance phenotype, etc.? And are you planning to using your bacteriophage adjunctive or as an add-on treatment with antibiotics? Or as stand-alone therapy?

And you want to consider the design of the studies in the context of the objectives of the overall development program.

That includes consideration of the dose you're going to use, the population that you're going to enroll in the study, and your product. I'm not going to talk too much about the product here because that was covered yesterday and is best addressed by our CMC reviewers. But your study design could incorporate elements that could help foster further product development. So, for example, you can have selective features of Phase 2 study design in your Phase 1 study in order to gather some preliminary evidence of effectiveness.

So, safety. Safety is a consideration always, throughout development, after development, but during development your safety considerations can include by are not limited to, you know, and a lot of these have already been discussed. But just briefly, the sensitivity of certain human tissues to components of the bacteriophage materials. Any toxic effects of product excipients or impurities. I know we discussed endotoxin and exotoxin quite a bit yesterday. What device or matrix are you using to administer the

product? And some of the other issues that were discussed, again at length yesterday, bacterial lysis, transfer of antibiotic resistance, any change to the microbiome. And as people have discussed, what the role of immunogenicity is in bacteriophage, not only in terms of effectiveness, but as well, whether or not this poses a safety concern. Any potential organ toxicity from any excipient or other issue with phage. Hypersensitivity reactions, including immediate hypersensitivity and also, perhaps, some delayed-type hypersensitivity reactions associated with that immunogenicity. And again, there are always other unknown effects that we can't predict or haven't observed.

So, when you're designing your clinical trial, you need to think about how you're going to collect the safety data. And what you want to be doing with assessment of the nature and frequency of these potential adverse reaction and an estimation of the relationship to the dose of the product you're giving.

And so, here are some considerations of things that, you know, you may want to collect. So, all clinical studies need to collect adverse events, including serious and medically attended adverse events, meaning adverse events that require you to see a physician. What criteria are you going to use for grading? There are some standardized scales, CTCAE or DAIDS that allow you to grade criteria. If you have a more healthy population, the FDA has a toxicity scale for vaccine studies in healthy populations. You also need to think about the criteria you'll use, and have your investigators use, to assess causality.

Laboratory data—are you going to collect clinical safety labs? Which ones? Are you going to collect anti-phage antibodies? When? How long are you going to follow subjects for adverse events? And how are you going to monitor any potential or identified risks for your product or that are specific to your route of administration?

And I've linked to, on these slides

there's a new guidance on IND safety reporting that's very helpful and gives you a lot of information about safety data collection in clinical trials.

And, you know, safety is going to be a factor in all aspects of your protocol development. And, as you progress, emerging safety data can inform late phase safety monitoring and risk mitigation measures, so this they evolve over time as you learn more about your product.

And there are a lot of approaches to risk management. This is just a sample. It's not meant to apply to every single product, every single development program for all of these, but just to give you a brief overview—rationale for dose and route of administration, which should be supported by preclinical data if available, eligibility criteria in terms of, you know, who's safe to involved in your study? Are you going to do staggered enrollment, such as a sentinel cohort that will slow down the first few subjects to be enrolled to make sure are no

immediate safety concerns? Are there going to be stopping criteria for review by a safety oversight committee, in the event of certain adverse events? Will you use a data monitoring committee or a board? And it's always important to be aware of those regulatory reporting requirements for safety events.

So, when you're selecting your dose, you want to consider the route of administration. And I know we've discussed some of these different routes. What are the data from relevant animal models of prior clinical experience with related phage therapy products? What PK assessments will be planned, if any, for making dose regimen adjustments? Evidence of bacteriophage replication at the site of infection, and what preliminary measures of effectives you'll consider.

And then, so, for your study population, again, this can evolve as development progresses. Alternatives to health volunteers in Phase 1 studies could include taking into account some of the potential risks and what preclinical data you have on

healthy subjects colonized by target bacteria who don't have active infections. Less severely ill patients with active infections or, depending on the appropriateness of this, target population with active infection.

And then, you know, available safety, PK, proof of concept data can inform, you know, expansion or changes in the subject population.

So again, I'm just going to briefly touch on this because, you know, I don't have time to go through everything in this talk, and we do have a breakout session specifically dedicated to clinical trial design. But some late-phase considerations are, you know, as I mentioned, whether or not you're going to use bacteriophage as stand-alone therapy or adjunctive therapy and some considerations when you design your clinical trial that's relevant to those types of study designs. You know, your comparator group, how you'll select standard of care, what's needed to support bacteriophage use as a stand-alone therapy? Who is an appropriate patient population to

receive that, how you'll manage development of resistance, etc.?

And again, these are some other select late-phase clinical design considerations. And certainly, you could spend the entirety of the three-day phage session on clinical trial design because it's complex, and, again, many of these will be specific to your clinical development program.

But just briefly, some of this has already been covered but, you know, additional elements to consider as you move into late phase, what your study endpoints are going to be? So, those need to be clinical endpoints that directly measure how a person functions, feels or survives. Whether or not you're going to also include microbiologic endpoints? How you're going to design the study to avoid bias? What your comparator group will be? How you'll configure the design of your study? What type of comparisons you're going to use, superiority, non-inferiority, etc.? And then, statistical considerations including, you know, sample size, how you'll define success

and, again, who you're going to analyze?

So, in the several minutes I have left, I just want to briefly touch on some FDA programs that we tend to get a lot of questions about. So, Expedited Programs for Serious Conditions —there's an excellent guidance on this linked to below, and it'll give you all of the details and information, and also provide a lot of definitions for these terms because a lot of these terms have a really specific, dedicated meaning in the context of expedited programs.

So, what is Fast Track Designation? That's when you have a drug that's intended to treat a serious condition, and that's defined, but, in general, I think the vast majority of infections that are treated with phage would likely meet this criterion. And that the nonclinical or clinical data demonstrate the potential to address an unmet medical need. An unmet medical need is addressed in that expedited guidance, and there's also specific guidance that's dedicated solely to unmet medical need and explaining what that is.

What does that get you? So, I think of this as like the gold membership. You get actions to expedite development and review, and you can also get rolling review of your BLA, which means that you can submit different sections of the BLA in a sequential manner.

When can you do it? Any time. So, this is any time your IND is first submitted or any time thereafter, before it receives marketing approval.

Breakthrough Therapy Designation–the criteria are a little bit different. The drug, again, needs to be intended to treat a serious condition. And then, here is what you need for this. Preliminary clinical evidence—so note that you need clinical evidence. You need to have moved into a little bit of clinical development of your product. And that the drug may demonstrate substantial improvement on a clinically significant endpoint over available therapies.

So, there's a lot in there and the definitions are very specific for each of these terms. You know, what substantial

improvement means, what a clinically significant endpoint is, and what available therapies are. And that's all, again, explained quite well in the guidance.

And what does this get you? Well, I think of this as the platinum membership. You get everything with gold, but you also get intensive guidance on efficient drug development, organizational commitment, and other actions to expedite review. And again, you can request this at any time, you know, after you submit your IND. But please remember, again, you need to have that preliminary clinical evidence.

So, just briefly, LPAD Pathway. This is a Limited Population Pathway for Antibacterial and Antifungal Drugs. This is intended to address challenges associated with conducting clinical trials to evaluate antibacterial drugs for the treatment of patients with serious bacterial diseases. And this is a streamlined development program that may involve smaller, shorter, or fewer clinical trials. And, I think, that the next

talk will address, you know, some considerations for clinical trial design in this context.

And, you know, there's some regulatory requirements for this. The drug is intended to treat a serious or life-threatening infection in a limited population of patients with unmet needs. Again, refer you to the unmet need guidance. There's a guidance specifically on this LPAD Pathway, and it talks a little bit about what FDA might consider a limited population and how that would inform the specific labeling of a drug that's approved under this pathway.

And, just lastly, one small plug for patient experience data. Recently FDA is working on four methodological guidances, which address in a stepwise manner, how stakeholders can collect and submit patient experience data. One of these is final, one is in draft, and two are in process. And these provide some information on how patient experience data can contribute to your clinical development program. Again, this

might address items such as, you know, PROs—patient-reported outcome measures—as well as clinician-reported outcome measures, that can measure the impact of your intervention on patients. And this can be important, I think, and most relevant in the chronic diseases that can, perhaps, be treated by phage, including chronic, you know, pseudomonal infection in cystic fibrosis patients or, perhaps, as, you know, Dr. Aslam referred to, prosthetic joint infection patient, et cetera.

So, just to sum up everything there, I think the future of bacteriophage rests on the initiation of scientifically rigorous clinical development programs that include adequate and well-controlled clinical trials to support licensure of bacteriophage therapy. And, just to let you know, that CBER is prepared to assist developers of bacteriophage drug products throughout their preclinical and clinical development programs. Thank you.

DR. SCHOOLEY: Thank you Dr. Reindel. We now have a five-minute break before we resume with Dr. Scott, who will be talking

about adaptive clinical trial design. So, please stretch your legs, and I look forward to seeing you in five more minutes.

I'd like to welcome everyone back and we're now going to resume the session with a presentation from Dr. John Scott from CBER. He'll be talking to us about an overview of adaptive clinical trial design. Dr. Scott?

DR. SCOTT: Thanks so much. Let me get my slides up. Okay, thanks again. It's a pleasure to be here for this workshop. I think this is a really important topic.

What I'm going to be talking about today is adaptive clinical trial design and adaptive features to designs that might facilitate development of bacteriophage products. This is kind of a broad overview of the whole topic of adaptive trial design. Not everything I talk about will necessarily be applicable to any one given development plan but just, sort of, as a menu of options to keep in mind as you're planning, especially later-phase clinical development.

I should say my name is John Scott.

I'm from the Office of Biostatistics and Epidemiology in FDA CBER.

So, just an outline. I'm going to start with a background for adaptive design and some introductory concepts. And a lot of what I'm going to be saying today—almost all of it—is kind of walking through aspects of things that are covered in this document. This is a Guidance for Industry that FDA published in 2019 on adaptive designs for drugs and biologic trials.

So, starting kind of most importantly, with a definition of what we do and, you know, kind of by implication, what we don't consider to be an adaptive design. In that guidance, adaptive design is defined as a clinical trial design that allows for prospectively planned modifications to one or more aspects of the design, based on accumulating data from subjects in the study. So, just picking that apart a little bit, there's a few key words—design, prospectively planned, and subjects in the study.

So, a couple things that implies are

not adaptive design are trials where—in any trial, where there are unplanned changes based on comparative interim results. That is, you do an interim analysis of some kind, the sponsor or the DSMB are surprised by something they see and want to make a change. In general, those changes should be discussed with FDA, and that is out of the scope of what we consider to be adaptive design.

And then also, study protocol amendments that are based on information from sources external to the study, are also not considered adaptive design. In many cases, these kinds of changes can be good and useful, although they also will often have to be discussed with FDA prior to implementation.

So, why adapt? Why do an adaptive trial design? There are kind of three categories of advantages for adaptation, and they don't all apply to every kind of adaptive design.

The most cited reason is to have advantages in the statistical efficiency of the trial. By statistical efficiency,

basically, what that means is having a greater chance of detecting a true drug effect at a given expected sample size. And we just kind of, sneakily threw the word "expected" into sample size because, once you're talking about adaptive design, you're usually not talking about a fixed, planned sample size but instead a range of possible sample sizes. So, expected means like average.

There also can be ethical advantages to adaptive designs. I think this is most well understood in the context of group sequential studies, where you might be stopping a trial if the data received so far aren't consistent with the idea that the drug is effective, that is stopping for futility. Or if you received early evidence of overwhelming effectiveness, that is stopping for efficacy.

Some adaptive designs can also provide advantages in understanding drug effects in being able to answer different kinds of questions about a drug. For example, you might have improved estimation of a dose-response relationship in an adaptive

dose-selection trial than you would in a trial where you just look at a couple discrete doses without an adaptive escalation algorithm.

There are also limitations of using adaptive designs. The first one I want to mention are the statistical methodological challenges that come in the context of ensuring control of the chance of erroneous conclusions and ensuring reliable estimation. So, there can be issues with bias, with the coverage of confidence intervals, and so on. I'll talk a little bit more about that later.

There can also be operational challenges in maintaining patient data confidentiality and trial integrity when implementing adaptive designs. And, in some cases, there can be challenges in the interpretability of trials due to adaptive changes that kind of by implication change the underlying scientific question of the study. This comes up, in particular, in studies, for example, where you might be adapting the patient population as the study goes on or the study endpoint, things like that.

There are a couple important distinctions to keep in mind. One is that the scope of what's possible and what has to be considered for exploratory studies, in a regulatory context, in particular, is quite different from what has to be considered for studies intended to provide substantial evidence of effectiveness, that is, studies intended to support licensure of a product. Really what I'm talking about today are the latter kind of studies.

Adaptations are quite possible in early phase and often very useful, but many of the considerations for ensuring statistical rigor and adequate interpretability of the trial, are of, you know, sort of like a less severe degree with earlier phase trials.

Another important distinction are analyses that are based on comparative analyses of accumulating study data versus non-comparative analyses. This is—roughly corresponds to what's more often called unblinded versus blinded interim analyses. There's a, kind of, light distinction between

comparative and unblinded. We prefer comparative. In general, when you're doing adaptations that are based on comparative results, that can and generally will affect the operating characteristics of the trial. By which we mean things like the Type I error probability and the bias of estimation. And these methods generally require special statistical handling, whereas the non-comparative analyses more often do not.

Okay. So, key principles from a regulatory perspective. We've outlined in the guidance, kind of, four laws for adaptive design—four key principles to keep in mind when planning and proposing an adaptive design. One is that the chance of erroneous conclusions should be adequately controlled. Two is that estimation of treatment effects should be sufficiently reliable. Three is that details of the design should be completely pre-specified. And the last is that trial integrity should be appropriately maintained. I'm going to talk in a little bit more detail about each of those.

The first for controlling the chance of erroneous conclusions—what we're looking to do here is to limit the chance of making bad decisions. And bad decisions can be caused by incorrect conclusions of safety, incorrect conclusions of effectiveness or, conversely, incorrect conclusions of lack of safety or lack of effectiveness for a drug that should go forward to the next stage but, due to problems in the trial design, would not.

In general, effectiveness in an adaptive trial design is typically supported with tests of null hypotheses. Generally speaking, these are conducted as one-sided tests at a 2.5 percent significance level. It's important to note that a lot of adaptive designs applied naively can inflate Type I error probability. And so, it's important to use testing methods with error probability control that go with those adaptive designs. And that error probability control can either be supported by statistical theory or, in some cases, by comprehensive clinical trial simulation.

The second principle was ensuring reliable estimation. So, it's really critical that we have accurate and precise estimates of treatment effect in order to make sure that our regulatory decisions are based on reliable benefit-risk evaluations and to give appropriate labeling for patients and providers to enable the practice of evidence-based medicine. An issue with adaptive design is that certain adaptations can lead to biased estimates and incorrect confidence interval coverage which means that, for example, a 95 percent confidence interval isn't actually a 95 percent confidence interval.

So, what FDA recommends is that whenever possible, people use statistical methods that adjust estimates for bias when those methods are available. For some adaptive features those kinds of methods aren't really available, and we recommend that, in those cases, sponsors instead evaluate the extent of bias and make sure to interpret and present their study results cautiously.

The third general principle was complete pre-specification. In general, prospective planning of an adaptive trial should include the anticipated number and timing of interim analyses, the type of adaptations, the statistical methods that will be used at the interim and final analyses, and the anticipated algorithms governing adaptation decisions.

Having good pre-specification is really key for several reasons. For one thing, it helps make sure that you're using appropriate inferential methods for the adaptive design you've chosen because you're thinking ahead about it. It also increases confidence that adaptive decisions that are made aren't based on accumulating knowledge in an unplanned way, which would generally lead to Type I error probability issues that may not be resolvable. It's only the adaptations that are based on knowledge in a planned way, where we can make appropriate adjustments for Type I error inflation.

And then, finally, just sort of from

an operational perspective, pre-specification helps motivate careful planning. It reduces desires that sponsors might have to look, you know, to peek at comparative interim data. And, in cases where the DMC is involved in the adaptive design process, it helps ensure that the DMC can focus on their primary mission of ensuring patient safety and trial integrity without having to give a lot of careful thought to what comes next in the adaptive design.

The last principle that I mentioned was maintenance of trial integrity. It's probably pretty well understood that having access to comparative interim results in a clinical trial can wreak havoc in a number of ways. And, in general, that access should be limited to people who are independent of the personnel conducting or managing the trial. This helps provide greater confidence that any potential unplanned design changes aren't motivated by having peeked at accumulating data. And this is true for every trial. It's not specific to adaptive trials. The issue

with adaptive trials is that there can be additional challenges due to the scope of the interim data analyses you might be conducting.

Having knowledge of interim trial results can affect a number of features of the trial in negative ways, including patient accrual, adherence to the protocol, treatment assignment in some cases, retention of patients in the trial, and even endpoint assessment, depending on who is doing the assessment and who has access to the interim results.

Okay. So, just a brief word about the blinded analyses, adaptations based on non-comparative analyses. So, what we're talking about here is usually called blinded sample size re-estimation. So, in general in a clinical trial, the sample size of the trial is going to depend on your significance level, on the power you're targeting, on the effect size you're targeting or that you believe you have, and then, also, on what we call nuisance parameters, which is anything that we don't really care about, but which affects the

statistical comparisons themselves.

So, if you're looking at an outcome variable that is measured on a continuous scale, that would include the variance of that endpoint. If you're looking at a binary endpoint, it might include the event rate on the control arm, which, for the purposes of estimating the treatment effect, may not be of intrinsic interest but certainly affect how many people you need to recruit into the trial.

A problem is that, at the design stage of a trial, there's often considerable uncertainty about these factors. And so, the goal of these blinded sample size re-estimations is to use accumulating information about the nuisance parameters—for example, interim estimates of the variance—to modify the sample size to maintain power at a desired rate if the nuisance parameter—for example, your control rate is less than you thought it was—if the nuisance parameter suggests you need more people.

Okay, a bit more about adaptations

based on comparative results. So, the most important category of adaptive design, overall, are group sequential designs. So, these are designs that allow stopping the trial early for efficacy or for a lack of efficacy—futility—or, in some cases, for harm in order to better address ethical and, kind of, pragmatic or financial issues of the trial.

Some advantages of these designs—it can help avoid unnecessarily exposing trial participants to inferior treatments, once we can be pretty confident the treatment is inferior. In cases where we're stopping early for effectiveness, it helps ensure that effective treatments are available to people outside the trial as quickly as possible. And then, in terms of the, you know, operational or financial benefits, these methods generally reduce the average sample size and/or how long the trial is, which also can accelerate the development of treatments, obviously.

And then there are a whole host of other kinds of adaptations that can be based

on comparative interim results. This includes other adaptations to the sample size. These are usually called sample size re-estimation methods. One method, in particular, that's becoming fairly widely used is called the promising zone approach where, let's say, midway through the trial or partway through the trial, you look at the comparative results, you do a calculation called the conditional power, which is, sort of, like an updated probability of trial success based on what you've seen so far. And then, based on what that tells you, you might add more people to the study. And, when done correctly, that kind of adaptation doesn't actually inflate the Type I error probability.

There are methods that adapt the patient population, things like adaptive enrichment, where, as the trial goes on, you start to identify who is responding best and focus on them for future enrollment.

There can be adaptations to treatment arm selection. This comes into play, generally, when you're talking about trials

with more than two arms. You might start with two investigational arms and a control and, halfway through, drop one of the investigational arms that isn't performing as well.

There are adaptations to patient allocation, what's called adaptive randomization. So, these can either start randomizing more people to the effective, more effective arm of a trial or can assign people to different arms based on baseline clinical or demographic covariates to help ensure balance in prognostic factors.

In theory, you can have adaptations to the endpoint that you're looking at. This is not really done in practice, it's just, kind of, theoretically possible.

And then, finally, it's not just, kind of, pick one and go with it. You can have a trial design that uses multiple adaptive features, which is often a good idea but does raise, obviously, further statistical complications.

These are things I'm not going to

talk about in any detail. They're all covered in the guidance document that I mentioned in the first couple slides. But I did want to mention just that these are additional things to consider in adaptive design planning. The use of simulations. Possibly using Bayesian Adaptive Designs. There are special considerations in Time-to-Event settings or when you're adapting based on a potential surrogate or intermediate endpoint.

Secondary endpoints—there are statistical implications there are as well. There are safety considerations and special considerations when you're talking about unplanned changes or changes based on external information.

Okay. And then, finally, the last thing I wanted to mention is just a couple other related initiatives or related regulatory topics. For one I wanted to mention there's an ICH group working on adaptive designs. So, ultimately, hopefully, we'll have kind of international consensus on best practices in this area.

And then I wanted to mention the FDA's Pilot Review Program for complex and innovative clinical trial designs. So, this is a program that people can submit trial design proposals to and the kind of quid pro quo is sponsors who participate in the program get more and more intensive interaction with FDA on the statistical features of their trial design, and, in exchange, the sponsor agrees that certain features of their design can be publicly disclosed as educational material for future trial sponsors. So, it's sort of meant to be kind of a win-win for the sponsor and the scientific community. So, we have a website for that, and there's also a guidance document that talks a little bit more about complex innovative trial design.

I believe I'm at time. So, thanks very much.

DR. SCHOOLEY: Thanks very much, Dr. Scott. And we'll now shift to *in vitro* assessment of phage therapeutics by Dr. Robin Patel, the director of the clinical microbiology lab at the Mayo Clinic. Dr.

Patel?

DR. PATEL: Good morning, everyone. It's great to see so many people interested in phage therapy. For the next 20 minutes, I'm going to talk about phage susceptibility testing in support of phage clinical trials.

We've been using conventional antibiotics for almost a century now and, as we know, the reason we're considering phage therapy is because of the crisis of antimicrobial resistance. But I want to focus on testing of therapeutics for antibacterial therapy.

Conventionally, antimicrobial susceptibility testing has been done and is done for a large number of antibiotics, antibacterial drugs, antifungal drugs, antiviral drugs, and so forth. And testing in the laboratory is a really important part of clinical practice, although it's not maybe very interesting for everyone and, a lot of times, we don't pay a lot of attention to the details of how that's done, sort of behind the curtain, if you will.

But it is a complex area. We have a large number of methods that are used, and there are specific methods that really apply to every species-antibiotic combination. And then, there are specific interpretative criteria that apply to every species-antibiotic combination. And we're always learning and updating and trying to make these types of results better.

So, we haven't completely figured out conventional testing of conventional antibiotics. We use broth microdilution. We use agar dilution. We use disc diffusion susceptibility testing. We use gradient strips.

In different regions of the world, different standard setting organizations oversee development of standards for antimicrobial susceptibility testing. For example, some of the players will include the Clinical and Laboratory Standards Institute in the United States, EUCAST in Europe, and I'm part of the CLSI. There are many committees within this group that look at how

conventional antibiotic susceptibility testing is done, and we have regular meetings. There are continuous updates to this. And just as an example, the document that you see in front of you, the M100 document, which is a document that outlines performance standards for antimicrobial susceptibility testing, is republished on a yearly basis with lots of changes.

So, this is a complicated area and has nothing to do specifically with phage susceptibility testing. But I think, for those who aren't directly involved in testing of antibiotics and methods of susceptibility testing, it's important to recognize that this is complex. And yet, here, obviously, we're dealing with chemicals and bacteria. When we get into phage susceptibility testing, the equation becomes a lot more complicated. And so, I'm going move to talk about that, but I think it's important to keep in mind where we are with testing of regular antibiotics.

So, as phage therapy is being considered in human medicine, we have to think

about the concept of phage susceptibility testing, or you might use the term PST, to sort of match up with what we see with antimicrobial susceptibility testing.

And you might ask, well, why would we want to do this? Well, one is to select phage or phage combinations for individual patient isolates. This is, after all, what we do with conventional antibiotics. And so, we might test a panel of phage or a phagogram to select one or more phage for therapeutic use.

We might test patient isolates with fixed-composition phage cocktails. And then, if we don't find a suitable cocktail, test individual phages from a library of phages to find a phage that might work against that patient's bacterial isolate.

Arguably, if we had phage cocktails or broad-spectrum phage that could allow for empiric phage therapy, we might not need to test, but I think we're not really to that point. And then, when we have cases of resistance to phage, and we've heard about this type of situation today, we might retest

that phage to determine whether resistance has emerged. We do the same thing with conventional antibiotics, or if there are combinations that were involved in that particular phage therapy.

I want to tell you, briefly, about the Antibacterial Resistance Leadership Group Phage Taskforce. This is a group that has come together, with support from the National Institutes of Health and with involvement from members of the United States Food and Drug Administration to answer a number of questions regarding the clinical use of phage therapy. And the questions center around clinical use of phage therapy, pharmacokinetic considerations, and finally, laboratory testing. And it's that last piece that I have been most heavily involved in.

And I'm going to show you throughout this presentation just a smattering of some of the questions that we've been engaged in answering. There is a document that hopefully will be complete sometime in the very near future and submitted for publication. We were

trying to get at a guideline-type document. Obviously, it's hard to build guidelines in this area that's really just emerging and where we don't have lots and lots of evidence to base our recommendations on.

But one question that we asked is, under which conditions should laboratory-based testing be used to select phage for therapeutic use? And the taskforce considered that phage susceptibility testing should be considered to select phage for therapeutic use when phage therapy is being considered given that, even the broadest spectrum phage, including cocktails, do not cover all members of given species.

We recognize the dynamic tension between the logistics and turnaround time of testing. Those results are not immediately available. Really, it's the same thing for conventional susceptibility testing but maybe a little bit longer here. And we recognize that in acute infection, there may be a desire to use phage therapy very quickly as empiric therapy before results of such testing is

available. And that could make sense with then activity confirmed based on testing and any adjustments of regimens made at that point in time.

For chronic infection, it really makes sense to do that testing prior to administration of phage therapy. And of course, as I mentioned previously, to monitor for emergence of resistance in cases of therapeutic failure.

However, there are several knowledge gaps. There's no specific evidence out there that would look at whether one should use phage susceptibility testing. In other words, there are no trials, for example, comparing use or nonuse of phage susceptibility testing that would support the use of phage susceptibility testing like we might look at other evidence in clinical medicine.

Also, phage therapy, as mentioned today, is often being considered for some of our most challenging infections. So, this includes infections that involve biofilms or that may involve non-standard routes of

administration such as topical, inhaled, or injected phage.

I think it's important to keep in mind that, even with conventional antibiotics, most of our testing informs the use of systemic therapy—oral dosing or intravenous or IM dosing and not, for example, topical dosing or injected dosing. And so, that adds another level of complexity to phage therapy.

And then, also as mentioned, oftentimes we're thinking about using more than one phage together. And so, that brings up the question of testing more than one phage at the same time together. And, as also mentioned today, oftentimes phage are used alongside antibiotics and so that brings up the question of testing phage with antibiotics, which, again, adds even more complexity to this particular equation.

The ARLG Phage Taskforce then looked at the question of what methods are available for determining phage activity against clinical isolates and how should results be interpreted? These are straightforward

questions that we might ask about regular susceptibility testing, but we looked into what about phage susceptibility testing?

The taskforce identified many laboratory testing strategies for assessing phage activity against individual bacterial isolates but noted no standard in the field. Despite the lack of clinical validation of *in vitro* susceptibility testing—in other words, correlation with clinical outcomes—the taskforce considered that it may be reasonable to assume that a lack of *in vitro* phage activity against a targeted bacterium may correlate with poor clinical outcome. But I will talk more about a caveat about that a little bit later on.

So, what about phage susceptibility testing methods? We lack standardized, clinically available methods for phage susceptibility testing and specifically, methods that demonstrate a correlation between that *in vitro* susceptibility testing and clinical efficacy. Of course, we understand that clinical efficacy is in process of being

addressed and defined.

We also recognize that, as with conventional antibiotics, methods for phage susceptibility testing could vary by bacterial species and by phage. This, obviously, will bring a lot of complexity to phage susceptibility testing.

There are two common general methods that are used for phage susceptibility testing. One is monitoring of bacterial growth in liquid media. And the other is the use of phage with semisolid or solid media to look at lytic activity.

We also lack interpretive criteria. So, what do I mean by that? Well, with conventional antibiotics, you know, we traditionally measure an MIC or a zone of inhibition around a disc. But that's not the final answer. We have to take that information and interpret that into a category of susceptible, intermediate, susceptible dose-dependent resistant, and report that out.

And many labs actually don't even report MICs. They'll just report out those

interpretations. We certainly only report that if you're doing disc diffusion. But we, of course, don't have interpretive criteria for phage susceptibility testing, and this may vary by infection site. It may vary by infection type. It may vary by bacterial species. It may vary by phage. And it may vary by phage administration route. So, this is quite a complex area when we're thinking about phage susceptibility testing.

Also, there is a convention of measuring the multiplicity of infection or MOI, the ratio of phage to bacteria. And it's important to consider that we don't know the number of bacteria that are present in individual patient infections. That's not something that's measured as a standard in clinical practice, and as a clinical microbiologist, I would submit that that would be somewhat challenging to do. It is also likely to change over time. We also know, of course, that phages will amplify in the host, and so, the dose will hopefully increase *in vivo*, but that makes it also challenging to

figure out the MOI.

So, let's take a look at some of the methods that are out there. Here is an example of a lytic/plaque phage susceptibility testing method. This is a double-overlay plaque assay. Here you take a mixture of phage lysate and bacterial inoculum in an overlay agar, and pour that over an underlay agar, and then incubate that, and look for quantifiable clearing for plaques as they're shown over here. You see two different plaque morphologies, and that signals the presence of infectious phage.

There's a modification of this where you can do the double agar overlay with your bacteria and then drop or spot the phage on top of that lawn of bacteria. And so, you can test multiple phage at the same time. In this example, we're testing 16, and you can see various different morphologies here of activity. And then, some spots, which are here, here, and here, where you see no activity. So, this is another way of assessing activity.

And then, there are liquid examples. So, what you do is a little bit more like broth microdilution if you will. You take your phage and your bacterial inoculum, and you look at whether there will be growth of your bacterium over time. And that can be done by monitoring OD, or that can be done by monitoring metabolism. And there are a variety of ways of looking at this.

One way that can be done—and this is being developed by APT—is to do what's called PhageBank Susceptibility Testing, where you take your phage stock, and you take your bacterial inoculum, both quantified to a specific quantity. You put them together in microtiter well plates and monitor for growth on a Biolog instrument over time. And you look at the amount of time that elapses before you see a signal indicating bacterial metabolism. So, this is another way of doing phage susceptibility testing.

And then you could envision, for example, using quantitative PCR with broad range phage primers targeting conserved

regions of individual or multiple families of phage to measure the amounts of phage over time, and hence, evidence of lytic activity in an *in vitro* assay. And then we might also envision genomic phage methods where, perhaps, we could take bacterial sequence data and predict activity. That's quite futuristic, but this might be another method that could be used.

However, back to standard phenotypic phage susceptibility testing. As with antimicrobial susceptibility testing, we likely need to standardize phage concentrations, the compositions of liquid or solid media, the incubation temperatures, durations of incubation, bacterial inoculum densities, the growth phase of bacteria being tested, what quality control strains are used, and, obviously, how to interpret results.

We need methods to quantify phage for laboratory testing that will distinguish viable from non-viable phage, because, obviously, if we're doing phage susceptibility testing, the phage need to be viable. And

then, we need quality control processes to test phage activity.

This is challenging, given the biological nature and potential for evolution of phage. The phage that are being tested in a laboratory need to be standardized. They need to be from a PhageBank stock of known titer, and processes must be put in place to mitigate changes in that stock over time, such as viability, concentration, or mutation. If that's not done, we'll really be testing something different over time. And this can be particularly challenging with newly isolated phage where there's not a lot of track record.

We also recognize that phage, like antibiotics, can adsorb to certain surface-types, such that labware used to handle them can affect the amount of phage present. And this can potentially be mitigated by the use of surfactant, Tween 20 or plasma.

So, I just want to show you some preliminary data. We've been looking at the APT method, just one method of phage susceptibility testing, and one of the

original first questions to answer is about reproducibility. If we do the testing in two different locations or more than two different locations, will you get the same results?

This is some data that's been submitted for publication. We did testing at APT and at Mayo Clinic, where I work, and we looked at 19 *E. coli* phages and 18 bacterial isolates, alongside 21 *Staph aureus* phages and 11 bacterial isolates. And overall, the percent agreement between testing at the two sites was 94 percent for the *E. coli* and 83 percent for the *Staph aureus* phage bacterial isolate combination. And we felt that was acceptable. This is not telling you that this a method that should or could be used, it's just really looking at can we get the same answer at two different sites?

There are multiple knowledge gaps around phage susceptibility testing. We need standardized, reproducible, "rapid," high-throughput methods. *In vitro* parameters that predict clinical efficacy need to be defined.

Some assays measure plaque

formation, as I mentioned, others growth profiles of bacteria in the presence of phage. We do not know if differences in plaque morphology or growth profiles can assess degrees of activity of phage, and we don't know thresholds for activity versus no activity.

We don't know whether there can be universal interpretative criteria that apply to all phage-bacterial combination possibilities or whether criteria will need to vary by bacterial species and phage type as we see with conventional antibiotic susceptibility testing.

And then, terminology—the ideal result reporting terminology, such as "active" versus "inactive," or "susceptible," "intermediate," "resistant," remain to be defined.

So, other knowledge gaps—we don't know whether different testing methods or interpretative criteria should be applied for initial versus on-therapy testing, where you might be looking for emergence of resistance.

And then, although we would assume that lack of *in vitro* phage activity against a particular bacterium would imply poor clinical outcome, phage could have enhanced activity in particular microenvironments in patients, in which they interact with their bacterial host. And these environments may not be represented by what we're testing *in vitro*. So, you know, we need to understand that.

It's also unknown whether we should test custom or fixed cocktails. For phage cocktail testing, we considered that each combination may be so unique to the individual patient's bacterium that generalization may prove challenging.

We don't know which methods will be best at identifying phages or phage cocktails that will be most capable of mitigating generation of phage-resistant bacteria.

And then, of course, we need to define storage and maintenance of phage that are used for phage susceptibility testing.

So, I'm going to end here. I probably raised more questions than answers. I

want to thank the ARLG Phage Taskforce Clinical Microbiology Subgroup. Members are listed here. The Mayo Clinic Phage Therapy Group and the Clinical Microbiology Laboratory pictured here at Mayo Clinic. And thank the NIH for their support.

DR. PLAUT: Dr. Schooley you're muted.

DR. SCHOOLEY: Oops, sorry about that. Thanks very much Dr. Patel. We'll now turn to the experience with CRISPR-engineered phages from Locus Biosciences by Dr. Dave Ousterout.

DR. OUSTEROUT: Thank you and good morning. Hopefully the slides are up okay. My name is Dave Ousterout and I'm the chief scientific officer and one of the cofounders of Locus. We are a company helping commercialize phage therapeutics using CRISPR-enhanced bacteriophages. And today we'll share a little bit of our experience having recently completed a Phase 1b Trial evaluating a drug product called LBP-EC01, which has activity against *E. coli* in

colonized patients that have *E. coli* in their bladder.

Just to quickly give everybody a quick summary of Locus. So, we've been around now for about six years advancing this concept of how to use CRISPR to enhance the bactericidal activity of phage. We'll cover a little bit on that, and, just to give everyone, again, sort of a broad view, we have a number of assets in development with a range of partners including Johnson & Johnson, as well as BARDA, who is directly supporting the Phase 2 and Phase 3 clinical trials for this particular asset we'll talk about today, and CARB-X.

We've done quite well in the phage therapeutic space and have been big believers in how phage therapy can solve AMR as well as extend into different areas where bacteria are causing more than just simple infections. We've worked pretty diligently over the past few years to create many of the different things that are required to have a successful phage therapeutics company. We'll touch a

little bit on our manufacturing—how that's influenced our ability to tackle this Phase 1, a little bit more on the technology, and some of our experience.

The *E. coli* asset we're talking about today is really the first lead asset amongst a number of different programs we have ongoing. CARB-X is supporting, really, a paired product in *Kleb pneumoniae* that we're now in the middle of really completing toward GMP stage. Johnson & Johnson also has licensed two other products that are in respiratory and bloodstream infections that, of course, we expect to advance in the coming years.

Just to dig in and get everybody familiar with a little bit on the way the technology works for Locus—it’s a bit of a unique tack. And the first component really is that it is based on bacteriophage. We leave the bacteriophage genome relatively intact other than introducing CRISPR-Cas cassettes, based on a unique enzyme called Cas3. That's the second mechanism that occurs in the way this drug product works.

Cas3 is actually a complementary system to Cas9, in that it exists in bacteria as an immune system as Cas 9. However, the way it acts upon DNA—unlike Cas9, which cuts like a pair of scissors, Cas3 is an exonuclease that cuts more like the Pacman depicted here. When directed against the bacterial chromosome, this nicely results in, essentially, death of that cell owing to permanent damage to the chromosome that isn't repaired, given this unique exonucleolytic mechanism of action.

Putting the two together has really been a unique and differentiated approach for us, both in terms of the activity of the phage, but also in the way we think about what it's doing. So, it is piggybacking on these obligate lytic bacteriophage. So, in theory, when injected into the cell, it does not persist. And as we have developed the data over time, what we're understanding is that the bactericidal activity of phages is sometimes limited by more than just receptor-mediated interactions.

As we all know, there has been a paucity of research in this field for quite some time, and, in particular now, the rise of genomics is helping us understand quite a bit more about the phages and (inaudible) of their interaction with the host. So, these mechanisms really come together to elucidate that fact—that, essentially, phages can transduce with a non-productive infection. And with Cas3, this results in improved bactericidal activity of those phages.

So, really, this is about maximizing the underlying potential of lytic phage therapy, while also retaining the core aspects of being able to be lytic and replicate.

We'll focus a lot today on the initial asset, which, again, we call LBP-EC01, which is targeted against recurrent UTIs. This is just a brief history as we've been developing this drug. About 2018—so, roughly three years ago—we established the first preclinical model demonstrating the activity of this product delivered either intravenously or by intraurethral administration. For the

purposes of the Phase 1, today we're going to talk a lot about intraurethral administration on the basis we observed in these preclinical studies that sufficient dosing could be achieved.

And we followed this up with a Phase 0 to really understand the patient population in the particular trial sites we were going after. And, in particular, to understand what was the prevalence of *E. coli* in these patients as we're going after a narrow-spectrum product. We, actually, are going to talk a lot about how we're using colonized patients. So, to understand how these patients are tracking over time as they're persistently colonized by *E. coli* as well as other potential uropathogens.

This allowed us to also confirm the sensitivity of a drug product in LBP-EC01, which is a composition of three phages in a fixed-cocktail format, as well as understand the MDR prevalence in the target patient population of the Phase 1.

And we submitted that data package

in 2019 to the FDA. We are regulated by CBER vaccines as other phage therapeutics. Received IND approval towards the end of 2019 and began ramping up in 2020 for about a 30-patient study evaluating first-in-human safety for this recombinant bacteriophage platform.

We'll talk quite a bit about—this is obviously a pretty challenging a pretty challenging year. We were able to successfully begin the trial. We paused during COVID, ramped up as soon as we were able to, ended up over-enrolling about 36 patients into the trial, and really some nice data we'll be able to share with the field today. We're very excited to demonstrate, for example, phage amplification in the human urinary tract.

These data have really set up the next phase of development and we plan to begin Phase 2 toward the end of this year, beginning of next year, and advance from Phase 2 into Phase 3 as the data matures.

That's the brief overview of really where we are as a company and this asset. We'll dive a little bit more now into the

Phase 1 and some of the considerations we had in the beginning of the clinical program.

Sorry, I hope you can see this. So, the mathematical modeling component of this really became to the forefront. So, when we took our preclinical data, we first asked the question, well, what is the dosing schedule for planning to go in with the reverse-flow catheter? How many doses, how long, and how long should we clamp?

Really not a ton of data available out there as to that potential effect, and so, we used a series of models based on both *in vitro* and *in vivo* data that we fed into this. And a couple really unique observations here. The first, we thought that mathematical PK modeling could be a valuable tool where there is a lack of clinical and translational data. I think the second part of it is, with these models—and they are consistent with what we see in preclinical settings—BID dosing was apparently going to be effective in these models.

The other part, which is a unique

aspect I think as we've been talking about this morning, the bioburden in the patients is going to play a role in the outcome of treatment, both in terms of driving amplification of the phage when administered as well as suppression in emergence of resistance.

What these are essentially telling us is that a clamping time of 30 minutes would be sufficient to allow interaction of the phage with the bacteria in a closed compartment like the bladder, as well as multiple doses BID—and this informed, really, the seven-day selection of BID dosing—in order to ensure the opportunity to crash this population over time depending, of course, on the variability of the amount of bioburden present in each individual patient.

The other part of this, that's paired to this, is our manufacturing facility. We actually had a Phase 1 facility we had purpose built to support this trial and have since followed up to create a Phase 2 at a small scale commercial capable facility. Both

able to handle, under the FDA and EMA regulations—and thinking a lot about how phages need to be made to high titer, very low endotoxin, and high purity away from residual host contaminants, led us to invest in a about 14-million-dollar facility. It's state of the art and actually won facility of the year award recently.

We're very proud of this aspect because we recognize that GMP in bacteriophage is a quite difficult proposition. So, going forward, we expect that, especially from a clinical perspective, the ability to create high-titer phages with well-characterized contaminants and impurities is essential to the success of creating fixed cocktails in these programs.

Diving a bit into the study design. So, a fairly unique study design. This is a placebo-controlled, randomized, double-blind study, randomized 2:1 to receive LBP-EC01 alone or placebo—in this case is vehicle, Lactated Ringer's. As I mentioned before, based on some of our preclinical analysis, we

chose to go into the bladder directly via reverse-flow catheterization twice a day through seven days and then subsequently evaluate at day 14 and 28 to understand the full PK/PD effects—but really looking at safety as a primary endpoint at the end of the study.

So, in this case, the primary endpoints of safety as well as pharmacokinetic analysis were designed to help us understand, of course, that recombinant bacteriophage can be safely administered as well as understand the amplification profile of the underlying phage.

We enrolled patients that were greater than 18 years old and had a history of UTI but were asymptomatic though being persistently colonized. We think this is a pretty unique aspect to this trial as we really wanted to be able to understand target engagement of the phage and, of course, in a monotherapy setting if possible—hence the choice going to an asymptomatic patient population.

We didn't allow for antibiotics in the prior 14 days against Gram-negatives in order to prevent confounding of that result. And, beyond that, we really put together a series of secondary endpoints to look at how the pharmacodynamic effects we're following for this particular type of administration.

A little bit on the inclusion/exclusion. So, we were allowing indwelling urinary catheters with intermittent catheterization. We did allow patients that were receiving some type of antibiotics for things that are not related to Gram-negatives, and we did allow for the presence of other colonizing uropathogens in these asymptomatic patient populations but required that *E. coli* be the predominant uropathogen.

And I think it's important to note that, because of the way we chose to go after this different patient population, it is a mix of both complicated and uncomplicated UTI patients. Really what we were after here is demonstrating target engagement and phage amplification.

Pretty complicated pharmacokinetic sampling schedule here. We looked at both blood and urine. Again, the product is delivered directly into the bladder, so urine is where we expect most of the activity to occur. We did also want to evaluate if there was any systemic exposure from this particular administration. But again, looking for—heavily on the pharmacokinetic analysis, as well as taking sufficient sampling to understand potential pharmacodynamic effects and impact on the uropathogen.

Diving into the results a bit. So, in the safety and tolerability, this is just a high-level piece of it. Now, we did see , essentially, it was very tolerated. Pretty safe. Overall outcome—no AEs that were attributed to LBP-EC01 directly. There were two nondrug related SAEs. One in the active, one in the placebo arm that both resolved by the end of the trial. We'll dive into, one of these was one unsurprisingly COVID obtained as in an outpatient setting. There was no splenomegaly. We'll talk a little bit about

our interactions with the FDA in looking for splenic changes based on some preclinical findings out in the field.

We established proof of mechanism—really, the goal of this trial was to look at pharmacokinetic effects of phage amplification in a controlled setting in these patients. And some exploratory analysis that is linking pharmacokinetic effect with a pharmacodynamic effect, because as you expect, PK/PD is expected to be linked for an active amplification agent like bacteriophage.

Beyond that, we're quite encouraged by some of the exploratory analysis demonstrating that particular pathogens like ST131, which are heavily drug-resistant, appear to be more responsive *in vitro* to our drug product and correlating to some case studies within this Phase 1 population that are quite encouraging.

And finally, in the pharmacodynamic effects—though this trial wasn't designed to measure this, and the patient population as asymptomatic—we did see a reduction in

colonization relative to placebo. I'll talk a little bit about the unique aspects of that when we see the data. And we did see a benefit of treatment versus placebo.

Just going through some of TFLs here. So, the first component is, we didn't observe an outright safety signals of interest. Really clean profile for this drug product, despite being a very challenging patient population. It did include some patients with pretty significant medical histories, complicated UTI.

As I mentioned, we did see a couple of non-drug-related SAEs here. The first of which is we did have a coronavirus test positive subject. Obviously, in the middle of 2020 in executing this trial, we had a lot of different safety protocols in place that have been modified. Before we restarted the trial, it appears that the subject had just, unfortunately, contracted the virus outside of the clinical lab setting.

We did also observe pneumonitis in another patient, although this was deemed to

be consistent with their prior medical history and not drug-related.

The other part I had mentioned is that we had looked at splenic changes. We did have some preclinical observations, particularly related to monitoring endotoxin levels and how they may impact changes in, essentially, splenomegaly. We developed an approach to, not only use palpation to determine any splenic changes, but also look at ultrasound. And as—very happy to report that, while there were some changes that were in palpability, none of these were considered to be significant. They all did resolve and, given their balance between the groups, were not deemed to be drug-related.

This is a TFL, now diving into the amplification data—the pharmacokinetic data in the patient population shown on a linear and semi-log scale. We'll dive into maybe a different visualization of this, but what we were quite encouraged by is the very beginning of the trial was essentially designed to have a single dose that was we then followed up at

six and 12 hours after that dose, before giving the second dose, giving us a chance to observe in these patients if there is phage amplification. These patients are persistently catheterized, and, beyond the clamping of the 30 minutes after the initial dosing, they're actually allowed to freely urinate. So, the expectation is these patients, over the course of 12 hours will, of course, be evacuating their bladders and producing more urine. Which, without amplification, the ingoing hypothesis would be you would see clearance of the bug—I'm sorry, of the bacteriophage.

And, in this case, we actually see persistence of the phage, and that's denoted by the mean of the group shown in the red dots, as well as the individual patients. We're actually seeing sustained phage levels in the bladder through 12 hours prior to the second dose, which would be indicative of amplification.

Moving forward and doing a secondary analysis of this, we looked at patients and stratified them by those that had *E. coli*

burdens greater than 1E6 CFU/mL at baseline versus those that had less. This should give us an ability to see, of course, that if there is significant amplification of the bacteriophage, you would see a difference between these two groups in this exploratory analysis.

Worth noting, we put in the bacteriophage at approximately 10 to the ninth PFU/mL in aggregate. So, about 1:1:1 stoichiometry of the three phages. And we did see an increase in overall levels that corresponds to greater presence of a potential host. So, this is really nice evidence demonstrating a host and concentration-dependent amplification of the drug product. But, interestingly, also in the group that has less than 1E6, you'll note that the C-trough does not hit zero. Actually, it is sustained at a level that is related and correlated to the amount of bioburden in the human urinary tract at baseline.

So again, demonstrating quite nicely that we are seeing amplification of the phage.

We are seeing this pharmacokinetic profile that you might expect from being able to have an active amplifying agent.

Looking at the pharmacodynamic data here is the TFL. This is really interesting data to unpack. Again, not a the trial that was designed to look at microbiological outcomes in this asymptomatic patient population, but the first thing we'll note is that, upon catheterization, and despite receiving placebo administration, these patients actually began to have an increase in baseline of their *E. coli* levels. Whereas, when treated with LBP-EC01, we did see a decrease in the initial dose that is sustained through the dosing period. And we'll note that, obviously, these go back to baseline after removing catheterization and treatment, which we believe is what you might expect as these are persistent, colonized patients.

A different way to look at this data was also to understand which patients had improved, consistent, or deteriorated levels from baseline. And this, again, shows very

nicely the bifurcation of different treatment groups.

We defined "improved" as a reduction in at least one log from baseline. "Consistent" as within, being within one log, and "deteriorated" as an increase over one log. And saw, again, a bias toward LBP-EC01 being able to either reduce colonization or sustain it, whereas the placebo treatment group began to have an increase upon catheterization.

One interesting patient we wanted to throw out in a case study—and this is last slide—is the link between the pharmacokinetic and pharmacodynamic effects. So, in this one patient, we see nicely that there is a consistent pharmacokinetic signal with amplification as the organism is present. We lose the organism, and then you shift to a PK profile that looks consistent with the absence of the organism. And in this case, between the doses, you're seeing clearance of the phage, and then at dosing, obviously, you have the phage administered directly to the bladder.

That's actually the last slide, and I appreciate the support of BARDA, the FDA, and a lot of people on our team and our subjects, patients, and physicians that have helped us get here. I don't think we're doing any Q&A, but thank you again for your time.

DR. SCHOOLEY: Thanks very much, Dr. Ousterout. We will be having a Q&A this afternoon. We're going to have lunch now for half an hour and then resume with three more talks, then have the panel discussion at the end. So, please enjoy your lunch. I look forward to seeing you in a few minutes. Thank you.

(Recess)

DR. SCHOOLEY: Okay. I'd like to welcome everybody back from your lunch break, and we're now going to shift into three more presentations before having a panel discussion. The first presentation will be by Dr. Robert Hopkins from Adaptive Phage Therapeutics, who is going to tell us about their approach to addressing antimicrobial

resistance with their adaptive library of bacteriophage. Dr. Hopkins.

DR. HOPKINS: Okay. Can you hear me okay?

DR. SCHOOLEY: Yes, we can.

DR. HOPKINS: Okay. Thanks, Chip. My name is Bob Hopkins. I'm an adult infectious disease physician, and the Chief Medical Officer at Adaptive Phage Therapeutics. APT is a biotech company that's based in Gaithersburg, Maryland, and we've been in business for about three years now--2017. I'm going to talk about how to address emerging antibiotic resistance with adaptive phage bacteriophage. We refer to our bacteriophage library as PhageBank.

Just to put it in context, the WHO reports that excess mortality due to COVID-19 is over 4.5 million deaths, and this compares to about 10 million deaths per year predicted by the year 2050, related to AMR bacterial infections. There is no question, we've got a ways to move.

If you look at history of how

antibiotics are developed and used, we see a general trend where once they're licensed and enjoy widespread use, resistance eventually develops. We call this lather, rinse, repeat. This is seen for virtually every antimicrobial class. It begs for alternative approach. Bacteria will always find a way to develop resistance, and at APT, we're developing phage libraries for therapeutic use. These are continuously expanding, and the idea here is they will adapt to avoid resistance. And this adaptation can occur either at the individual patient level or at the population level through continuous surveillance of phage susceptibility.

Any solution to the AMR crisis must be better than the bacteria themselves. PhageBank includes a library of highly-curated bacteriophage that does just that. This approach, we believe, will drive adoption and ensure long-term commercial viability. While antibiotics have a critical role in modern medicine, there are at least three problems that stem from AMR, antimicrobial resistance.

The first, of course, is obvious, that resistance leads to obsolescence of antibiotics. This drives the need for more antibiotic development. However, even these new antibiotics are associated with toxicities, and their use is usually restricted through stewardship programs. This is needed to delay the development of resistance, but it is a never-ending cycle and is not sustainable.

This is particularly relevant given recent examples where new antibiotics were licensed but then were not deemed to be commercially viable. And it should be mentioned that most antibiotics also have poor antibiofilm activity, unlike bacteriophage, which have evolved alongside bacteria for many, many years, and they both have lytic as well as antibiofilm activities.

We are initially focusing our PhageBank on three indications of prosthetic joint infections—we're doing trials of prosthetic joint infections, diabetic foot osteomyelitis, and also recurrent chronic

urinary tract infections. We're also providing clinical trial material to the NIH for their sponsored CF trial and are working with Oyster Point in an ophthalmologic indication. All these clinical trial programs are supported by our phage susceptibility testing assay that we refer to as the host range quick test, HRQT. This test here is a critical complement to implementation of any phage library approach for both our clinical trials, our emergency INDs that we partner with, as well as our commercial plan.

The concept of using personalized phage libraries was initially published by our Chief Scientific Officer, Carl Merrill, in a 2003 Nature Review paper when he was at the NIH. His concept on how to operationalize phage libraries was continued by his protégé, Dr. Biswajit Biswas, and both are in attendance today. Dr. Biswajit Biswas is the chief of the phage lab at the Biodefense Research Directorate, BDRD, under the NRMC, the National Medical Research Center. This went on for about ten years where the Navy

developed a large collection of bacteriophages that are isolated from multiple environmental sources across the world. They were interested in commercializing this library, and APT acquired the rights back in 2017. We have a patent pending for the manufacturing methods that allow for the production of highly-curated clean phage that are sequenced, annotated to remove any deleterious genes, such as AMR-resistance, toxins, or lysogeny. We also have recently entered into a collaboration agreement with WRAIR, who has an active phage program.

So, why are we focusing on natural phage? I don't need to tell this group that phage are, basically, nature's most prolific bacterial killers, and their ability to replicate at the site of infection increases the dose at the relevant site with each replication cycle. The phage library is a broad-spectrum solution, even though each individual phage is very narrow spectrum. Unlike the off-target effects from antibiotics, this narrow spectrum allows us to

target pathogenic bacteria without harming the commensals. And, finally, natural phage are considered GRAS, Generally Recognized as Safe, and can be administered and have been administered using a variety of routes, including intravenously.

One of the keys to success will be to build an ever-expanding phage library, and we've partnered with a number of groups, including the NRMC, BDRD, WRAIR, and other collaborators to continuously build our collection of phage in our PhageBank. In addition, in the last year we've built in-house capability for phage hunting, and we have experienced scientists in the identification as well as testing of phage. These collaborations and in-house expertise will allow us to continuously fill any gaps there may be, or particular indications, or particular pathogens, for clinical use or clinical trial use.

I'll also note that, you know, the speed at which these folks have identified phage through phage hunting, they go out to

get sewage samples and others is pretty amazing, and, you know, the time to, you know, essentially the time to phage hunting is much different than the time for antibiotic screening and discovery which really allows us to expedite and enhance our PhageBank in a rapid way.

This slide just highlights the attributes of PhageBank. They're natural, as I mentioned. They can either be used as a single personalized treatment or a cocktail of personalized phage, again, in combination with our PST, phage susceptibility testing assay. So, essentially, the idea is that the PhageBank will continuously be enriched. The bank, itself, is polymicrobial nature but each one is very specific. The DMF allows us to efficiently develop our program, in that we just have one DMF and we are able to implement three different clinical programs cross-referencing to the DMF, which allows us to quickly move into the clinic, and then the precision approach allows us to be very specific and decrease the risk of failure by

testing pretreatment in the lab.

This is our phage susceptibility test. It measures—it essentially allows us to enhance the probability of success in clinical trials by assessing efficacy in the lab *a priori*, and this differs from any empiric use of either fixed cocktails or even antibiotics. This assay can be adapted to not only evaluate the kinetics of metabolic activity of bacteria, but also can evaluate antibiofilm activity, antibiotic synergy, testing as well as phage-phage interactions, as Robin had mentioned earlier today.

We have collaborations with both the Mayo Clinic and Robin's lab, and Hadassah Medical Center in Hebrew University in Israel to develop these assays, and it's going to be a critical component to our clinical development programs as we move forward. Currently, the phage susceptibility test is considered part of our manufacturing process. And we plan to work with the Mayo Clinic to develop it as a laboratory-developed test for commercialization at initial launch. I don't

need to—Robin gave a great talk earlier, and I don't need to embellish this, but the Mayo Clinic labs have extensive experience in supporting specialty laboratory testing as LDTs. They support over 4,000 healthcare organizations around the world. So, we think we've got the right partner in terms of commercializing this.

Next slide. So, this test allows for precision therapy. It not only allows us to be very specific in our treatment of individual patients, but it serves as essentially a surveillance platform to continuously optimize our phage library based on the epidemiology of phage susceptibility testing at individual institutions. So, at commercialization, for example, we're not planning to provide clinical just-in-time manufacturing. Rather, we plan to pre-position PhageBank that is specific to the approved indications and local phage susceptibility epidemiology. Hence, we can provide phage, an inventory to each institution that's very specific to that susceptibility pattern in that institution.

So, that's the beauty of it, and that's the idea, and we've already installed a number of PhageBanks. Essentially, this is a picture of our phage dispensing system. We've installed these at our clinical trial sites across the country for UTI and DFO, and this PhageBank is connected to a iPad device that has a PhageBank app. This app allows you to communicate the phage susceptibility test results to the pharmacist and directs the pharmacist on what phage to use and how to deliver it. And you can see here that the freezer has a number of boxes, each one with a number of vials. There can be up to 3500 vials per, what we call ATM or the PhageBank ATM, and it's monitored—it's got remote monitoring, it's got a bar-code scanner. So, you can confirm what vial you're picking. It allows us to monitor what's being removed, and it's fully self-contained, has its own hotspot, so that we're not relying on any internet connection, or anything like that. We've got a whole product development team that has put this together for our clinical trial, and

we're going to continue that for commercialization.

Here, I just wanted to go through some of the cases. I don't have time to go through all of them, but we have, essentially, you know, we've treated about 45 patients, 16 of these have been published, 13 different types of infections in terms of indication, and 10 different bacterial species have been addressed with phage coming from APT. I'll just review three of them.

This one is the well-known case, Tom Patterson that Chip Schooley initially treated, in which they got two different *A. baumann*ii cocktails for pancreatic pseudocyst, did full recovery within 48 hours, and then—sorry, improvement within 48 hours and then full recovery within 11 weeks. And it is the title of the publication of a book called "The Perfect Predator." If you haven't read it, it's a good read.

The next case I'll just review was the case one of our collaborators, Dr. Ron Nir-Paz, in the Hadassah University in Israel,

treated an unfortunate gentleman that developed osteomyelitis of *A. baumannii* and *Klebsiella* following trauma to his right knee. He developed a complete recovery following seven days of phage, and this is sort of the first example of where we're able to treat two different bacteria with two different phage and get cure.

And then finally, this is just another case that got us real interested in addressing the prosthetic joint infection indication. He's HIPAA waived here, but John Haverty had had multiple surgeries and multiple courses of antibiotics. I think he had 17 surgeries in the past prior to getting phage therapy. And he actually got, when he got phage he didn't get that with any surgery, jus intravenous phage, and the only antibiotic he had was oral minocycline; and this was a case treated by Dr. Gina Suh at the Mayo Clinic who's our collaborator there for PJI. This was remarkable in that there was no surgery at all, and he had enjoyed resolution from his *Klebsiella* prosthetic joint infection

up to two years now; and that he got this initial response here just over 48 hours.

This got us interested in PJI, and we've got programs put in place to assess a variety of different approaches for prosthetic joint infections using phage. There were eight other cases that we had treated under our emergency IND program. And this just summarizes the data that is provided to us from our collaborators at the University of Maryland, Dr. James Daub and Dr. Gina Suh at Mayo Clinic summarizing the different bugs that you tend to get, that they see in their prosthetic joint infections. And, essentially, what we're doing is we're targeting these bugs, initially targeting the *Staph* species and then moving down the list as the trial proceeds in order to address the majority of bacteria that are associated with prosthetic joint infections.

And then, finally, the regulatory path for PhageBank has probably been the most interesting thing in the last couple of years here at APT. We've gotten three INDs allowed

for the indications I mentioned earlier. We've received an orphan drug status for a prosthetic joint infection indication; and one of the more interesting aspects is allowing, you know, working with the FDA to get allowance to add additional new phage to our PhageBank for use in clinical trials. And, essentially, we are doing that for the trials that we have in place now. The *E. coli*, the UTI trial is focused on *E. coli* initially, but the prosthetic joint infection is much more broad, and we are going to continuously add phage to the PhageBank, assuming again, that the FDA reviews all the sequencing data, annotation data, etc., before use.

I'll just mention, you know, we always are focused on safety, but, to date, the safety profile for phage looks pretty good, and that does allow us to really try to address some of these other aspects of phage treatment, including getting proof-of-concept efficacy in these early studies. So, that's what our focus is as we evaluate safety in our Phase 1/2 trials.

And I thank you. I've had a lot of help along the way with the multiple collaborators. We thank everyone that's been helping us along the way.

DR. SCHOOLEY: Thanks very much, Dr. Hopkins. I appreciate that, and we'll now be moving to Dr. Jennifer Schwartz who will talk to us about phage therapy for managing *Shigella* infections, from Intralytix.

DR. SCHWARTZ: Okay. Can you hear me?

DR. SCHOOLEY: Yes, we can. Thanks.

DR. SCHWARTZ: All right. And my slides are up. Okay. So, I'm Jennifer Schwartz. I'm the Director of Clinical Development at Intralytix. Today, I'll be talking to you about our efforts towards phage therapy for managing *Shigella* infections.

Intralytix is a clinical stage biotech company.

Dr. PLAUT: Dr. Schwartz, your slides are zoomed in.

DR. SCHWARTZ: Oh, no. How did I do that?

AV OPERATOR: You want to stop

sharing and share again?

DR. SCHWARTZ: Sure. Better?

AV OPERATOR: We see your presenter view. Click on display settings.

DR. SCHWARTZ: Okay. I don't think this bar will be much of a problem on. So, Intralytix is a clinical stage biotech company that develops phage products for human and animal use and food safety applications. Our facility in Columbia, Maryland has state-of-the-art high-throughput robotics, large-scale phage manufacturing and commercial scale phage spray-drying capabilities.

Intralytix has a number of clinical phage products targeting a number of clinically relevant organisms, one of which is *Shigella*, which we all know is a major worldwide cause of morbidity and mortality; and the second leading cause…

DR. PLAUT: I'm sorry to interrupt, but we're seeing your presenter view rather than the full slide show.

DR. SCHWARTZ: Okay. Is it still the presenter view?

DR. PLAUT: No, we're good.

DR. SCHWARTZ: Okay. Well, let's continue. So, why *Shigella*? Because it's important; and it's, you know, has increasing prevalence of multidrug resistant organisms, as well as prevalence in food and recent large outbreaks, and from recent reports of sexual transmission of the bug.

So, phage therapy can provide an alternative approach for reducing the severity and incidence of shigellosis. Intralytix has developed a *Shigella* phage preparation that has progressed through pre-clinical development. The phage preparation is called ShigActive, and it has received a generally recognized as safe for GRAS notice from the FDA for human consumption and food safety applications, and it's sold under the trade name of ShigaShield. It's a cocktail of five lytic bacteriophages that specifically target all four serogroups of *Shigella* with overlapping efficiencies.

Our phage preparation doesn't contain any of the undesirable genes that we

look for during manufacture, as well as no intact or viable prophages. We also show that it does not mispackage the DNA and it's unable to undergo generalized transduction.

So, to have a significant impact on *Shigella* indications, a polyvalent treatment covering the most common serogroups is necessary. And so, our ShigActive product has 90 percent lytic potency against over 100 *Shigella* strains in our collection. The collection includes strains that are all clinical shigellosis isolates that have been isolated from geographically distinct regions of the world and also represent a collection from the CDC of multidrug-resistant strains.

So, an optimal five-phage cocktail was chosen using our proprietary phage selector program. A simplistic explanation for this bioinformatic pipeline is that it assesses all known phage pairs and selects monophage combinations with the highest efficiency and broadest spectrum. Shown here on the right is a force directed graph where each green circle represents one of the

monophages, and all of the smaller blue and orange circles represent different serogroups of *Shigella* strains. You can see there're some overlapping efficiencies. There are redundancies within the monophage, but there also some monophages that have a unique kills.

Just shown here is just, if we break out a number of strains that fall within this collection that fall within each serogroup and their efficiency of killing by our cocktail. Did we lose my sound?

DR. SCHOOLEY: No, we hear you.

DR. SCHWARTZ: Okay. I had a big beep in my earbuds. Okay, so, I figured we could just add another issue. To access the efficacy in a mouse system, BL/6 mice were challenged with an *S. sonnei* strain before or after phage treatment. And shown here is the *Shigella* burden in fecal pellets or in cecal samples, one or two days after phage treatment—or after challenge, I should say. So, all phage groups decreased the *Shigella* burden in the fecal pellets and in the cecum, but the best performing was the dark green group, which

were provided phage one hour before and again one hour after *Shigella* challenge. After one day of treatment, we see at least a one-log reduction in *Shigella* burden, in fecal samples, and by two days we see close to two logs reduction.

Just an overview or summary of all of our preclinical proof-of-contact studies. Our *Shigella* phage preparation provides 100 percent protection in HeLa cell invasion assays. What I just showed you in the previous slide is that *Shigella* shedding was significantly reduced in mice pretreated with ShigActive compared to a placebo control, and it was equivalent, or possibly superior to ampicillin in other groups at reducing shedding of *Shigella* in the fecal and cecum stool samples. That data is published as well as the next two bullet points, where we saw little to no impact on the normal gut microbiota compared to ampicillin in mice, as well as in the repeat-dose toxicity studies, we saw no toxicity using body weight, health, and toxicity measures.

So, we proposed to use an oral administration of ShigActive to manage shigellosis and a continuous, double-blind placebo-controlled, randomized Phase 1/2a clinical trial, using a human challenge model.

So, our project is led by Dr. Sandro Sulakvelidze who's the PDPI on a NIAID funded U01 clinical trial award, titled Bacteriophage-based Approach for Managing *Shigella* Infections, with the goal to perform proof-of-concept Phase 1/2a trials to look at the safety and efficacy of ShigActive. The aims of this award are to produce the ShigActive clinical trial material, develop and submit the regulatory filings and gain approvals, as well as conduct the Phase 1/2a trial.

Our clinical trial and microbiome partners are at the University of Maryland School of Medicine, at the Center for Vaccine Development, or the CVD. Dr. Wilbur Chen, Dr. Karen Kotloff are our clinical PIs, and Sharon Tennant and Marcela Pasetti are our lab PIs. Dr. Claire Fraser, who is the Director of the

Institute for Genome Sciences, will lead the microbiome effort for this study.

So, while the increasing number of compassionate use case studies has been reported, there's still few—as we've been mentioning today—still few randomized controlled clinical trials. And of those that have been recently reported, only seven report oral dosing. Three of them are case studies, and four are clinical trials. So, given that *Shigella* studies are primarily anecdotal historically or have only been reported in Russian literature, we wanted to leverage important lessons from a recent unsuccessful and related trial, the Bangladesh *E.coli* phage therapy trial reported by Sarker, *et al.* in 2016, in which they orally administered a phage preparation for a diarrheal indication targeting *E. coli*. So, Dr. Brüssow, the senior author on the study, published a failure analysis highlighting the numerous flaws of the study, and, I think, you know, based on some of what Dr. Aslam said this morning, many of these traits are still common in more

recent studies as well.

So, specifically, these flaws are that this particular trial wasn't powered to detect a treatment affect. It only achieved a 50 percent enrollment, and of that, only 50 percent of the cases of acute diarrhea had confirmed *E. coli* infections, which they confirmed after the fact. And then to reduce the power even more, the phage cocktails that they used only had 50 percent coverage for the *E. coli* isolated from these patients.

Also, another flaw was that the majority of the acute diarrheal infections were polymicrobial, and similar to what Dr. Aslam said earlier about the PhagoBurn study, this trial also had suboptimal phage doses, where they estimated over 1,000-fold lower than their intended target dose. So, the reason for this reduction wasn't known but one of the hypotheses was the lack of neutralization of gastric contents during dosing, which the Bangladesh regulatory entity did not allow as part of their dosing regimen.

So, we believe we can overcome, at

least, this last obstacle given Intralytix's long history of manufacturing high quality, high titer phage products and through the use of bicarb administration during dosing.

So, by employing a unique study design, we can also mitigate some of these other issues that some of these other failed trials have seen, to allow for better assessment of our phage therapy product, where the experimental human challenge model proposes a promising tool to assess efficacy under a highly controlled environment, with a defined inoculum and easier management of the signs and symptoms. And so, there are a number of existing CHIMs available, but the ones that target bacterial indications are those against *Vibrio cholerae*, *Campylobacter jejuni*, ETEC, and *Shigella*.

Unfortunately, not all of these failures can be fully tested in this type of trial, but our controlled inpatient human challenge model and dosing protocol can overcome many of these. One, by using the highest practical and allowable dose,

administering the doses with bicarb to neutralize the stomach contents, using a single known pathogen challenge with known susceptibility to the phage cocktail. And so, while these are artificial settings, it will help demonstrate the proof-of-concept that phage therapy targeting *Shigella* with ShigActive is both safe and efficacious in a human system.

So, in the Phase 1 portion of the clinical trial, our aim is to assess the safety and tolerability of *Shigella*. In this trial, there's no formal hypothesis, but we use descriptive statistics. It will be a single-site trial designed as a placebo-controlled, double-blind, randomized trial in 10 healthy adults with a 4:1 treatment to placebo ratio, where the sample size is intended to rule out rare unacceptable toxicity before proceeding to the Phase 1 portion.

So, this is a schematic of the proposed safety trial design. There's a 45-day screening period, followed by randomization

into two groups, one that receives ShigActive and one that receives the placebo. The patients will self-administer three doses of phage per day for seven days, and then they'll be followed out to 90 days post enrollment. The objectives here are to assess the safety and tolerability of the ShigActive product when administered orally at 10^{10} PFU per dose, as I said, three times per day for seven days. And the co-exploratory objectives are to determine the impact of ShigActive on the fecal microbiome, as well as to evaluate the quantity and duration of shedding of the study product.

So, assuming all safety criteria are met in the Phase 1 continuous trial, the Phase 2 portion will proceed. And the goals here are to assess both the safety and efficacy of ShigActive to reduce shigellosis in a human challenge model. Again, this will be a single site at the CVD. It's a placebo-controlled, double-blind, randomized trial in 42 healthy adults with a 1:1 ratio, treatment to placebo ratio, that will be divided into three

individual cohorts.

The expected duration is about eight months, which includes the 45-day screening period and a 12-day inpatient stay, followed by a six-month follow-up period. The study product here will be the same dose as Phase 1, which is 10^{10} PFU, orally administered three times a day after 90 minutes of fasting and one hour before meals, for six days. These doses will be co-administered with bicarb to neutralize the stomach contents, and the placebo here will be PBS with the same dosing regimen. The challenge strain that we will use will be a freshly harvested *S. flexneri* 2a strain 2457T, which is diluted in PBS to reach the desired inoculum, and this challenge strain is registered under another FDA IND; and this will be administered only once on day two and also co-administered with bicarb.

Shown here is the schematic of the Phase 2 trial. Again, we have a 45-day screening period. There's then a two-day acclimation period prior to challenge to ensure compliance by the subjects, because we

don't want to give them *Shigella* and have them not comply to the inpatient rules and policies. Prior to challenge, they will receive three doses of blinded study product, either ShigActive or a placebo. On day two they will receive a single dose of *Shigella*, and then it will follow by another five days of placebo or ShigActive. They are all administered three times a day and separated by about eight hours apart. On day six, the subjects will then be given three days' worth of antibiotics, and then prior to discharge, they must have a certain number of *Shigella*-negative stools, separated by at least 12 hours apart. If they don't, then they will continue to receive antibiotics until they become negative. Once they're discharged, then they will be followed up for six months.

So, this says endpoints, but it should be objectives. So, the objectives here are to assess both the safety and the efficacy of ShigActive in reducing the frequency of clinical shigellosis in this challenge model.

The secondary objectives are to

evaluate the efficacy of ShigActive in reducing the frequency of moderate to severe clinical shigellosis, and also in reducing the severity of shigellosis. We're also going to look at how ShigActive is able to reduce fecal shedding of the challenge strain following challenge, as well as we have several exploratory objectives to evaluate the quantity and duration of the study product, and to determine the effect of ShigActive on the development of both systemic and mucosal immune responses to the challenge strain following challenge.

So far, we have for this trial, the U01 Award, we've progressed through manufacturing in the pre-IND stage and are about to submit the IND. And so, enrollment at the CVD is expected to be in quarter one of 2022. So, I just would like to thank all of you for your patience with my technological challenges, as well as the workshop organizers for inviting Intralytix to present today. Our partner is the Division of Microbiology Infectious Diseases for the U01 Award. Our

clinical trial collaborators at the CVD and the IGS, as well as—this is an old photo, and we've grown quite a bit since our grand opening in the end of 2019—but certainly want to thank all the hard work of our R&D manufacturing and quality groups, without which we wouldn't be able to do these studies. Thank you.

DR. SCHOOLEY: Thanks very much, Dr. Schwartz. We'll now have one last talk, staying in the gastrointestinal theme, with Dr. Minmin Yen who will talk about phage prophylaxis for cholera; after which, we will have a panel discussion. Dr. Yen.

DR. YEN: Great, hi, everyone. I hope all of you and yours are staying safe and healthy during these times, and thank you to the organizers for the invite to present our work here today. So, I'm also testing out the live subtitle feature of PowerPoint, so, thank you in advance for your patience. We'll see how effective they are. Just trying to increase accessibility for our talks here.

So, my name is Mimi, and I am the

CEO and co-founder of PhagePro. We are a pre-clinical biotech startup in Boston, and our mission is to help the world's most vulnerable communities prosper using innovative phage-based solutions. And one of the core motivations for the recent surge in phage therapy, and for all of us here today, as many of us have talked about, is antibiotic resistance. But what I would like to do today with my talk is reframe that epidemic through a different lens.

If you've seen me or Dr. Tobi Nagel from Phages for Global Health speak at one of these conferences before, this map will look quite familiar to you. So, it is showing the proportional number of deaths from antibiotic resistance in 2050. So, one of the talks previously highlighted that if nothing is done about this, we'll have 10 million deaths per year by this period. But what I wanted to do is look a little bit more at de-aggregating the data and showing where these mortality rates are highest and where they are lowest.

So, here on this map, the light blue

is the lowest mortality rate and purple is the highest mortality rate. And as you can see here, the antibiotic resistance epidemic will affect Africa and Asia the most, especially in resource-limited settings where communities are more vulnerable to these infections, and as we note from the ongoing COVID pandemic, infectious disease reveals the cracks in our global healthcare infrastructure, and also illuminates how critical it is we act as a global community to address these issues.

What happens in Africa and Asia undoubtedly affects us here in North America and in Europe. So, we need to build up a flexible and adaptable infrastructure and pipeline of alternative antimicrobials that work as prophylaxis and as a treatment.

In addition, we cannot take a siloed approach to this. We have to understand the roots of the antibiotic resistance crisis beyond the pathogen dimension, and also take a more holistic approach in our solutions. And I'll talk more about this at the end in terms of what that means for our work here at

PhagePro in particular.

So, when we think about global health indications then, we're looking for three critical factors to make it suitable for resource-limited settings. So, one, it has to be specific to not add additional evolutionary pressure to antibiotic resistance mechanisms. Two, it has to be easy to distribute. So, anything that would make it more convenient for either the patient, the healthcare worker, or the government, or organizations responsible for healthcare delivery. And examples of this would be independence from cold-chain infrastructure or different routes of administration to reduce that burden on healthcare workers or, also, to increase patient compliance as well.

And last, but not least, it must be affordable. So, this can be seen through multiple levels. So, we can think about the individual doses themselves in terms of their pricing, and depending on the indication, it can also mean the cost of the campaign. So, we can think about the economics of prevention

versus treatment, since investing in prevention will be more cost-effective than treatment, both in terms of finances and human lives.

So, phages hit all three of these criteria. And as a team here at PhagePro, we evaluated our strengths not only in terms of scientific knowledge, but as I mentioned earlier, these in-country partnerships are critically important as well when it comes to taking something successfully out of the phage to the community and the patients that you're trying to help. Since we are a spinout from the Camilli lab, which is focused on cholera, the work at PhagePro is focused on using phages as a prophylaxis for cholera in a phages-for-all approach. And for us, and I'm sure for many of us here who have followed the history of phage therapy and have been in the field for quite some time, it's also a nice circle given the historic beginning of phage therapy where it was first started as treatment for cholera patients in communities as well. So, I'll talk a little bit about

cholera first to describe what we're looking at here and why it's so urgent that we need something for it. It's an acute, severely dehydrating diarrheal disease that can kill within 12 hours of symptoms appearing. So, the WHO estimates that there are 1.3 billion people in the world at risk for cholera, and without rehydration therapy, the fatality rate for it is approximately 40 percent, and half of those deaths will occur in children under five.

This is largely due to infrastructure issues and hygiene and sanitation, because the primary mode of transmission for cholera is water contamination. So, for example, this is a picture of the toilet that I had taken in a cholera-endemic area where the water, or the waste, excuse me, flows into a nearby stream where the community gathers its water. What has been increasingly recognized is that household transmission also plays a huge role in cholera transmission as well. So, in particular, for cholera, 80 percent of

secondary cases during an outbreak are due to person-to-person transmission, and it's really rapid. So, household contacts will come down with cholera symptoms within two to three days of the index case. And these people know how to protect themselves, but they're simply not given the means to do so. So, this is where we think phages, if we do it in a deliberate and impactful manner, we think this is a great way for phages to be a solution to disrupt household transmission.

So, something I would like to point here with cholera, in particular, which would be of interest to this audience is the also the clonal nature of cholera epidemics. So, from the scientific point of view, it's particularly attractive as a proof-of-concept for phage prophylaxis because we are able to hopefully cover a lot of the epidemic strains that are going on geographically around the world with one fixed cocktail, as we begin to build up this infrastructure and this pipeline that we will need to address more complex epidemiologically diseases.

So, all three waves of the cholera pandemic begin from the Bay of Bengal and spread locally, and this characteristic, although great for initial foray into phage prophylaxis, can also make it very dangerous. We are starting to see XDR strains of cholera in countries such as Bangladesh and have seen it spread to a number of countries in Africa over the past couple of years.

So, when it comes to our solution then, our phage cocktail, which we call ProphaLytic Vc, or PVC for short, includes three distinct vibrio phages, ICP1, 2, and 3, with distinct receptors and mechanisms for the virulence factors of cholera. And ICP1 even has its own CRISPR/Cas system, using a classical mechanism that bacteria use to protect themselves actually against the bacteria themselves.

So, PVC can provide immediate protection, which is greatly needed for rapid intervention measures to stop household spread. It's specific for cholera bacteria and does not contribute to existing mechanisms of

antibiotic resistance. And the ideal formulation that we are working towards is an oral tablet that can be self-administered and does not need to be kept in the cold chain, so that storage and distribution are simple. And, as I mentioned before, this is a priority for many of the stakeholders in global health that we have talked to.

I want to emphasize this point because as opposed to other regions of the world, being stable, and hot and humid temperatures is of particular importance to the global health product development. And we can see this issue play out even with the current storage requirements for code vaccines. Context for the distribution of the product is of equal importance to the science behind the product itself. So, for us, cold chain infrastructure is simply not reliable in places where people are dealing with cholera epidemics, and often the burden for cold chain storage is shifted to the community healthcare workers who are on the frontlines. Therefore, PVC has to be formulated into a stable oral

tablet if we want it to be of actual use in prevention of cholera outbreaks.

In addition, we need to think about the context in which cholera thrives. So, during a cholera epidemic, the easiest distribution method, and the most convenient one is the one that will be most effective. So, tablets are easy to distribute, and if we can have it be self-administered without the assistance of the healthcare worker, it can be even more widely and rapidly distributed, which is of increasing importance for cholera epidemics.

So, using the liquid formulation of PVC, we have tested it before in proof-of-concept studies, and we've shown in two animal models of cholera—the infant mouse model and the infant rabbit model—that PVC can decrease *Vibrio cholerae* colonization and prevent onset of symptoms. So, what we're showing here is the rabbit model, which is the gold standard in the field, since animals also experience the same symptoms of cholera that humans do. So, here in this rabbit experiment, we orally

administered a liquid formulation of PVC, waited three or 24 hours, then challenged the end mark with *Vibrio cholerae* orally, and monitored the animal body weights and clinical symptoms until the endpoint of the experiment.

So, in black here we can see the group that did not get PVC, and within 10 to 12 hours the animals lost between 10 to 20 percent of their body weight due to diarrheal symptoms. So, very similar to a human progression of this disease. For the PVC-treated groups, both the three and 24 hours they were much healthier and protected. So, unfortunately, due to the nature of the infant rabbit model, we were unable to continue dosing, but we hypothesize that PVC will be used as a daily dose for the 10-day high risk when done for household contacts of cholera, although that will be confirmed in a future human clinical trial. And what we're continuing to do now is develop a household transmission model using rabbits to model more realistic conditions in the community and testing the efficacy of PVC to disrupt that

transmission.

As we all know, one of the most important parts about looking to phage for either prophylaxis or treatment is understanding its phage resistance profile. So, thank you Dr. Plaut yesterday for the shout-out and for the quick primer to the data that I am showing here today. We looked at the phage resistance profile of the *Vibrio cholerae* isolates coming out of these infant rabbit experiments, and what we have found is single or double resistance in particular to ICP1 and 3, and no resistance to ICP2.

In addition, we did not find any isolates that were resistant to all three phages. We then sequenced these isolates to understand the phage resistance mechanisms and found them to be all receptor-minus mutations, and I'll talk about why that is of particular importance for us because the receptors are all virulence factors of *Vibrio cholerae*. So, for ICP1 and 3, they target one of the main virulence factors which is the O antigen—that’s the lipopolysaccharide—although, using

different mechanisms and different lifestyles. So, ICP1 is very specific to O1 which is by far the dominant strain in terms of causing epidemics around the world. Some of the mutations we found in the isolates coming out of our animal experiments are the ones that you see highlighted here in terms of the O antigen synthesis genes.

ICP3 also uses the O antigen but is more promiscuous than ICP1. So, it has broader coverage than just the O1 strain, and some of these O antigen mutations you see here will result in ICP3 resistance, but some of them were not. More importantly, when we tested these in an animal model in competition assays, these mutations all resulted in avirulence of the *V. cholerae*. So, for a bacterium, they are caught between these two evolutionary pressures, phage infection and avirulence, meaning that if there's evolution away from our phage infection, those bacteria are incapable of causing infection in the following person, which is great from the lens of disrupting the secondary transmission.

If we look at ICP2, it targets another virulence factor of *Vibrio cholerae* which is the major outer membrane porin, OmpU. And we've identified a number of point mutations and duplication mutations in OmpU and its regulator, ToxR, from some of our clinical samples that also contain some low levels of ICP2. When we moved these mutations into an isogenic background with our wild-type, we found that they confer ICP2 resistance, as you can see here from these EOPs. The OmpU mutations were mapped onto loops that were exposed on the surface of *Vibrio cholerae* and do not prevent formation of OmpU on the outer membrane surface of the bacterium. As you can see on this Western blot of outer membrane extractions from these different strains. ToxR mutations result in a disruption in regulation of OmpU, so ToxR mutants do not have OmpU on the surface, and they are resistant to ICP2 as well. So, with these mutants as well, we've done a variety of competition assays and found that, under certain conditions, these also are avirulent

as well. So, all of the phage resistant mutations that we found have, indeed, contributed to avirulence in our animals models.

So, some of our next priorities that I highlighted before is a solid dosage formulation, that's really critical not only for the temperature and humidity stability I talked about before, but also for stability past the stomach. So, as Dr. Schwartz talked about earlier, in the Bangladeshi trial at the ICDDRB, that's also the site that we plan to hold our first inhuman clinical trials given our strong in-country partnerships with the team there over the past two decades. So, due to the ethical regulations there, we are not allowed to use a buffer or a bicarb to allow passage of PVC past the stomach acid, because once you increase acidity of the stomach, then you're actually reducing the protection that human has to all of the diseases, not only our cholera indication that we're looking at. So, the solid dosage formulation will allow stability of PVC to get past that barrier in

order to reach the small intestine where *Vibrio cholerae* will colonize.

The second aspect is host range coverage. So, even though we know that cholera epidemics are clonal, we still want to look at the geographical distribution of these different isolates and have been collecting them from different countries over the past couple of years, in particular in Bangladesh, to make sure that our product can, indeed, cover the different geographic epidemics of cholera.

And, lastly, we're solidifying our in-country partnerships. So, again, in global health, this is of particular importance especially as a U.S.-based organization working in vulnerable communities, we want to make sure that our product has the right context incorporated already into the product development stage, even in the pre-clinical time, to make sure that it will be accepted by the community, and also a lot of the aspects that might lead to failure in the community are already addressed and known about at this

stage given the collaborations, insights into what those issues may be.

So, what I wanted to end on last, in particular for cholera, is this holistic approach. So, as we are starting to really shift towards this idea of having a more horizontal approach to controlling epidemics, what that means is looking at all the different aspects of what causes an epidemic. So, the WHO strategy for controlling cholera doesn't just include vaccines, it also includes surveillance. It includes water and sanitation, and hygiene campaigns. It includes social mobilization. So, remembering that we shouldn't just rely on scientific and technological advancements, but we should be working in conjunction with all of these other aspects that look at the socio-economic aspects of a disease in understanding how we can integrate our scientific approach into what is already being done on the ground by frontline workers.

So, with that, we think that there's a possibility for phages or a rapid acting

prophylaxis to become part of the strategy for controlling cholera in conjunction with the other approaches in the toolkit to holistically manage cholera outbreaks. So, hopefully, our work here provides a primer. We're setting up these in-country partnerships to establish a strong infrastructure for phage in these countries where antimicrobial resistance and deaths are going to hit the hardest, so that we can start to address more complex diseases in the future. So, I'll end that here. Thank you so much for listening. Thank you for NIAID for most of our funding. We were fortunate enough to receive a Phase two SBIR and R21 funding this past year and are happy to answer more questions about that as well. So, looking forward to hearing from all of you. Thanks.

DR. SCHOOLEY: Thanks very much, Dr. Yen, and all the speakers. Let me ask them to—all of you to reassemble here for our panel discussion, those of you who are still here. Let's see what we have here. We have Dr. Patel and Dr. Yen; Dr. Schwartz; Dr. Scott; Dr.

Hopkins; Dr. Reindel. And let's see, do we have Dr. Aslam, or not?

DR. ASLAM: Yes, you should. I'm here.

DR. SCHOOLEY: Okay, great. The Hollywood Squares are assembling here. All right. So, I have a number of questions. I think you all have been seeing the question and answer periods, too. I'll go through a few of these and see if we can get a discussion going.

One of the common questions has to do with route of administration. Dr. Aslam talked about a lot of intravenous administration. We heard about intravesicular administration from Dr. Ousterout. We heard about pulmonary administration, oral administration. How is this all going to sort out? Are we going to be using different routes of administration for every—each type of infection or will we gradually coalesce with more consistent approaches?

DR. ASLAM: I can take a stab at that, and I’m sure others can jump in. I

think, you know, the approach really depends on what we're trying to treat. So, if we're really targeting pulmonary infections in CF, for example, I think it makes sense to use an inhaled approach if we show that it is effective. Personally, I think, IV therapy—you, it's not that easy to setup for an outpatient's use compared to say oral therapy or inhaled, or topical. So, I think, it really kind of boils down to the indication and that sort of determines the route of administration.

DR. SCHOOLEY: Let's ask Dr. Ousterout. Do you see an intravenous role for your synthetic phages at some point?

DR. OUSTEROUT: Thank you. I actually brought my colleague, Dr. Paul Kim, he's our chief development officer. He wasn’t able to join earlier, but I dragged him in for the Q&A, and I’ll toss that one to him.

DR. KIM: Yeah, actually, we do see, you know, IV being valuable route of administration moving forward. We’re actually transitioning from the intraurethral route in

Phase 1 to an IV, proposed IV route in Phase 2, so absolutely.

DR. SCHOOLEY: Great. Thank you. We have some questions too about laboratory aspects of this. One of them has to do with how you measure colony counts in bacterial samples that are obtained from sites of infection. Dr. Biswajit Biswas is asking about whether or not you need to worry about neutralizing the phage that may be present at the site of infection, when you obtain your samples and spend the time in getting them to Dr. Patel and her colleagues. Any thoughts about ways to avoid post-collection artifacts?

DR. PATEL: It's a really good point. You know, I'm going to take it back to conventional antibiotics because I like to frame it that way. You know, we always say collect the specimens for culture before you give the antibiotics. Chip, we know that doesn't happen all the time, but we have learned that if you collect the specimens for cultures while giving the antibiotics, sometimes the cultures are negative, and that

gives you a false negative result. And I would assume that the same could happen with phage therapy. So, you know, I think you have to do things in the right order. I assume you would get your cultures and then start phage therapy so it wouldn't be such an issue there, but if you're measuring colony counts on therapy for the purpose of the clinical trial or maybe in clinical practice to look at outcomes, that's an important consideration, and if there were some easy way to separate the two, that could be helpful. I'm not sure that would be a very straightforward approach. So, that certainly needs to be borne into consideration.

If you're talking about quantitative cultures, you know, aside from urine cultures and a small number of other culture types, we don't usually do that, but there could definitively be effects on quantities.

DR. SCHOOLEY: One of the things that Ry Young and his colleagues used to talk about, he always talks about the old-guard phagers is that they would stop phage antibiotic or bacterial interactions with

neutralizing antibodies to the phages they're using, and pointed out that was one of the challenges with collecting clinical samples. Obviously, you have to have neutralizing antibodies to the phages you're using, which adds one more dimension to the challenge of getting a clinical trial started, but it is something, I think, to consider.

Dr. Ousterout, one of the questions that has come to you is why the *E. coli* load increased in the placebo recipients, in the urine.

DR. OUSTEROUT: Yes, and we'll just go kind of back and forth here a bit on this. So, you know, one of the key questions is did we alter the colonization course by catheterization of these patients. So, certainly, we see, as you kind of watch the bacterial burden counts, as we catheterized the patients, there was a transient increase, and then as we removed the catheter, it essentially, went back to baseline, and these patients looked like they did at sort of their baseline persistently colonized bioburden.

And, so, I guess, the thing we've been discussing internally is it demonstrates somewhat the decolonizing effect of the phage in the setting, so, you know, that combined with amplification, which should, of course, result in the death of the target cell, we think we see the pharmacodynamic effect, but moving forward into the next indication, you know, it's a discussion that we're having. As we're looking at the IV route, it becomes less of a component of considering how this works.

DR. KIM: I would agree, and I think there's some evidence for the existence of reservoirs in both, you know, complicated UTI patients and these colonized patients. You know, that's why they persist, that's why they get re-colonized. And so, we do think, as Dave said, we think that we're seeing some evidence of that effect—that reservoirs can be recolonizing, the dynamics that can change from the act of catherization as well.

DR. SCHOOLEY: Okay, questions, a couple of questions for Dr. Schwartz related to the challenge of the oral administration of

phages. You talked a lot about the issues of gastric acidity. Are there other aspects of the gastrointestinal tract that are enemies to the phage stability that you have to consider?

DR. SCHWARTZ: I think the short answer is that we don't really know. I think that part of—like this workshop is highlighting, you know, where the gaps are and our challenges are moving phage therapy forward. So, you know, the question is do we know whether it can get to the right site, and I don't think we have good models to look at that. Certainly, we've done a lot of work with ex-vivo models, such as gut simulation models, that show that we can neutralize the stomach compartments and allow the phage to survive those compartments and move through the, you know, the small intestine into the colon. So, but we don't know the answer *in vivo*, and so, you know, I think, just the short answer is we don't know and we have to determine it empirically. And so, that's part of the reason why some of our objectives are to study, you know, the quantity and shedding of the study

product because, again, we don't understand, you know, the PK/PD aspects of phage therapy. So, I think, that will also help shed some light on how the phages are transiting through the gastrointestinal tract.

DR. SCHOOLEY: While we're on your PK/PD questions, are you're going to sample just in stool, or are you thinking about sampling in other parts of the GI tract?

DR. SCHWARTZ: For this particular study, we're just doing stool.

DR. SCHOOLEY: Okay. And did you have any bioinformatic tools you used to select the phages in the cocktail that you're using? Dr. (inaudible) is asking.

DR. SCHWARTZ: Yes. So, we use—it’s a proprietary in-house software program developed by one of our engineers. It's called PhageSelector, and it's what Intralytix uses to determine the composition of all of our phage cocktails.

DR. SCHOOLEY: Okay. And someone is asking about the *Shigella* model. Are there any ethical questions that you're concerned about

related to that? Dr. Gabard is asking.

DR. SCHWARTZ: Well, I think that brings up a lot of questions, right, because as physicians—I'm not one—but you first want to do no harm, so, I think, that, you know, you can say well the benefit's not to the subject, but you'd have benefits to the population in general overall. So, I think, there are a number of ethical questions that come up with any challenge study. Certainly, you don't want to do a challenge study on a disease indication that is not treatable. So, that's part of the reason why, you know, we ensure that the patients, after their challenge, are administered antibiotics and treated appropriately. There are criteria throughout the whole study that if the patients meet certain criteria or even ask for antibiotic treatment prior to the scheduled time, that they're given it, and, I think, the most important thing is informed consent and that the patient, or the subject, fully understands what's involved in the study and why they're doing it.

DR. SCHOOLEY: And the inverse to that question is another question. Is it physiologic to give the phages before the challenge?

DR. SCHWARTZ: Right. So, you know, phages can be administered prophylactically and therapeutically. Again, I think one of the goals of this study is to try to reduce the number of variables, in order to show proof of concept of phage therapy against shigellosis. So, we decided to administer them prior to *Shigella* challenge, which we certainly hope sets us up for success, but you then need to do—we don't understand when do phages need to be administered; how much you have to give; how often you have to give. What's the severity of various disease that the patient is experiencing before you—or after you give a phage challenge, or phage therapy. So, we're simplifying the variables in the study, but certainly, you know, overall, we would want to administer these in developing countries where *Shigella* is a major issue, but you can also envision a product that is like a traveler's

pill, or even if there's known *Shigella* outbreaks, you can prophylactically administer it to the general population.

DR. SCHOOLEY: Do you have any idea about what population size you're dealing with, with a natural *Shigella* infection and whether the cocktail can handle that in terms of selection for resistance?

DR. SCHWARTZ: No. I don't think we've done in-depth resistance studies, and, again, it will depend on the target. So, you have several different serogroups and, depending on the serogroup, you have several different serotypes. So, we certainly haven't examined all of the different possibilities in the different settings because, you know, at least here at Intralytix, we're limited to, you know, our *in vitro*, high-throughput robotic system at the moment, and we have collaborators that do some *in vivo* studies, but in the population at large we don't have the answers to that.

DR. SCHOOLEY: Thank you; and there's a question from Dr. Borin, for Dr. Ousterout,

related to lytic phages recombining into the host *E. coli* genome. Do you look for this or are you concerned about this with your CRISPR/Cas3 cassettes?

DR. OUSTEROUT: That's an interesting question. I guess I'll give two component parts. This is why we use the lytic aspects, natural lytic aspects of the phage. The idea being, of course, that you should not have sustained gene transfer in theory. There's really nothing that necessarily would make sense for the phage to recombine, and the idea is, of course, if you're getting recombination, you're actively expressing things like lysins that are in the phage.

In the other context, the CRISPR/Cas cassettes are broadly targeted to the host chromosome. We look for redundant coverage and conserved coverage, often in our drug products having at least three distinct targets that are 100 percent conserved in a pretty broad informatic library of the target organism. So, while it's certainly something that we've considered, we haven't seen anything to date

when sequencing, for example, any emergent escape mutants. But it's a nice question.

DR. SCHOOLEY: We have another question for you from Dr. Nir-Paz about whether or not one log 10 reduction is substantial enough to expect a clinical success in UTIs. I guess, added to that, your modeling was really quite elegant. Did your modeling suggest that changing the MOI or any other approaches to this might have given you a bigger reduction, or what the limits in your reduction were? Why were you not seeing more than that with the phage you have?

DR. OUSTEROUT: I'm going to ask Dr. Kim to answer that, and I did see that some folks were having a hard time hearing, we tried to move the mic a little closer.

DR. KIM: No, I appreciate the feedback on the modeling, and we do think it's important to at least attempt some mathematical modeling because of the complexity of clinical testing. We did test various MOIs in our modelling scenarios and did find, you know, MOIs around one being, you

know, best suited for kind of this clinical indication and route of administration. So, we were trying to achieve, or target, around that MOI. In the context of the urinary tract infection, that would mean somewhere between— you typically see CFUs per mL around 10^5 to 10^8 or so, and so we targeted, actually a product at 10^9 PFU per mL because of that. And so, I apologize the second part of that question.

DR. SCHOOLEY: It was really mainly around issues related to dosing or other things you might think from your modeling that would help you have a greater log drop in your targeted bacteria.

DR. KIM: Yeah. I mean, MOI is one of them. Dave had covered this earlier, that we were testing the various starting concentration of bacteria CFU input, and that had an impact in terms of overall effect and speed at which you see the overall reduction. Clamping was the other one. So, 30 minutes to 40 minute clamps seem to provide sufficient CFU reductions in the time period that we were

treating, as well as BID dosing. So, all of those things were modeled, variations of those. We went from, for example, single doses per day, to TID, dosing three times a day, and chose BID because we didn't see an advantage with TID dosing, for example. We did see the repeated dosing, so over several days, being advantageous. We didn't test shorter durations in that modeling effort. We have looked at that more closely as we approach Phase 2, but we chose seven days because of the modeling we did.

DR. SCHOOLEY: Okay. Thank you. Along those same lines, there's a question for Dr. Aslam about how long, how she decides she's treated long enough.

DR. ASLAM: I will say, at the beginning, several years ago, this was trial and error, as we weren't really aware of studies of how long is appropriate. More recently, I think, we've moved toward shorter durations of treatment. Part of it depends on what we're treating and what the normal antibiotic course for such an infection would

be. So, for pneumonias and UTI-type infections, we're now treating for about two weeks. For LVAD, cardiac device, you know, prosthetic joint infections, we're treating for six weeks.

I don't know if that's the right answer or not, you know, in terms of—I think this needs to be assessed in studies to see if this is an appropriate duration or could we actually even go shorter. In the setting that, you know, we're assuming these phage are replicating in the patient while that infection is present. So, over time, we've gotten shorter, you know, around two weeks or so, but, you know, I don't know if that's enough or too much.

DR. SCHOOLEY: Okay. I guess that's like the three bears, just too warm, too hot, just about right. All right. Dr. Hopkins and Dr. Patel, a couple of things that relate to your talks are emergence of resistance under therapy. What role do you see monitoring phage resistance in your target organisms, and are there ways to anticipate where the organisms

will go in terms of having the next phage in the bank ready to roll?

DR. PATEL: I can start. You know, I think we should anticipate the possibility of resistance emergence, but it does also go back to the patient. You know, we have an immune system, oftentimes phage are used with antibiotics. So, if the patient is improving, the patient is improving, and that's—even if there is emergence of resistance—might be all right. But for patients who are not improving on therapy, especially some of the chronic infections that Dr. Aslam mentioned, I think there's a role for retesting and looking to see whether there was emergence of resistance. And the concept, almost like conventional antibiotics, is that you hopefully would have tested not just, you know, one phage and shown that it's active, but a number of phage even at the beginning. You would probably have to retest them, right, down the road, even if they aren't being used, to confirm that they're active, but that you would then have some other choices that you could turn to,

faced with resistance.

Of course, we don't know exactly when phage therapy works, and so, retreatment, you know, is a complex question, right, but, conceptually, that's what I would envision.

DR. HOPKINS: Yeah, I would maybe just add, you know, from a strategy perspective, we have pretty much built into our DNA that we would implement adaptive treatment. That's actually the name of our company. And so, you know, from a personalized therapy, if someone fails clinically and then you can get a bug, even in the clinical trials, we would, actually, go ahead and if we've got the phage available, that is active against the resistant, now phage-resistant isolate, we would do an adaptive treatment. Now, what we also do are these, you know, Phase 0 or, you know, retrospective epidemiological studies at the sites, of the clinical trial sites, you know, even before you implement the trial. So, you can either, you know, pull the trigger on one or may two phage, you know, a cocktail of two that are

known to be active, and you know that the phage, the cocktail, the PhageBank that you have going into a clinical trial, you want to be able to optimize those phage for the isolates that you identified, retrospectively, before you actually go into the study. So, all of that is done to try and optimize initial success, and that if you get resistance on treatment then you have another option of plan B, in individual patients, to optimize success in those also.

DR. SCHOOLEY: So, a lot of clinical microbiology questions, here one from Dr. Ran Nir-Paz again. A lot of times chronic infections or infections of large organs like the lungs, you have multiple different strains present, how do you know which one to select to target your phage?

DR. PATEL: This is a really good question and it could equally apply to conventional antibiotics. What happens in clinical microbiology laboratories when a specimen is submitted for a culture, is that we typically grow more than one colony from a

clinical specimen. And you may or may not like to hear how this is done, but we look at colony morphology, and if we see differences in colony morphology, we'll work up each colony morphology for susceptibility testing for conventional antibiotics, and, perhaps, by analogy, phage, right. But you definitely can have different sub-populations, especially in subacute or chronic, or colonizing infections. We know that. So, you know, how can you overcome that? Perhaps by testing more than one colony. I don't know what the limit on that would be. Testing combined colonies might be another possibility. It's a good question and it's a complicated question, and when we talk about emergence of resistance—I mean in some cases those resistant sub-populations were likely pre-existing, and you're just selecting them out. It's a little semantics in some ways. It's a very good question, and I think we need to think about it as we design clinical trials for phage therapy.

DR. SCHOOLEY: Dr. Aslam, I would like to mention that you're concerned about

with one of your LVAD infections that was an issue.

DR. ASLAM: Yeah. I mean, I think, we've seen this more in the study of Gram-negative, you know, *Pseudomonas* infections and CF or chronic biofilm-related infections. So, at least, on our end, you know, when we evaluate patients for phage, ideally we get multiple cultures or, you know, isolates over time, which usually are present when we're looking at compassion use cases because they've had, you know, several episodes of treatment and culture positivity already. And our goal is to select a phage cocktail that is active against all these isolates, or at least the very drug-resistant ones, so that we don't, you know, make the patient worse. I think that's, you know, a very valid question in complicated clinical scenarios. And, you know, for one of my patients that's what happened. He got worse, he had septic shock but then resolved. But we just need to be very careful when we choose these patients and phages.

DR. SCHOOLEY: Some of the talks yesterday made the point, too, that the interaction among the phages and complex microbial environment in which they're operating are also hard to model and sort out, and, certainly, can't be duplicated in the laboratory very well, and we know from the experience that those of us in infectious diseases have with our colleagues in pulmonary medicine who treat cystic fibrosis, they often don't want to hear from Dr. Patel about what she finds in terms of susceptibility testing and just want to use what they have in the pharmacy. So, we don't sterilize everything. We sometimes have to. Perhaps, with prosthetic infections it's a bigger issue, with implanted devices, but for a lot of these complex infections, we really don't get everything with what we treat, for sure.

Dr. Yen, we have some questions about what your plans are for overcoming the liquid issue. What kinds of formulations are you thinking about to get to something solid?

DR. YEN: Yeah, absolutely. So, some

of the things we're thinking about, I think, really build on what Dr. Malek has talked about, what Dr. Vehring who, I think, is in the audience today has done before for Dr. Nagel when she was doing her phages in Kenya for a solid dose formulation as well. So, I think, it really all depends on what works for our phages. We haven't done yet a DOE study looking at temperature, looking at pH, and all those different factors incorporated into one situation. So, that's where we need to start off with just a very preliminary stability study to then really decide what is the best way of going forward. Is it lyophilizing, is it using some other sort of technology to have a solid dose? And, for us, what's really important as a factor as well is the cost, so what is going to give it us the most stable formulation in the most cost-effective manner so that we can keep the cost of these doses low.

DR. SCHOOLEY: And to continue with the cholera question, given the kind of sporadic nature of cholera outbreaks, one of

the audience members wants to ask how you are planning to do your clinical trial.

DR. YEN: Yeah, absolutely. So, there are two ways to think about cholera epidemics. One is the sporadic nature where like in Haiti it's the result of a natural earthquake or a natural disaster, or in the case of Yemen where it's really due to a civil war resulting in refugee camps. But there's also a great many number of countries that have cholera endemically. So, where we plan to do our first-in-human clinical trial is in Bangladesh, which has a very predictable pattern to its cholera epidemics. So, it happens twice a year, and also, with climate change, unfortunately, it’s also increasing the length of time that these cholera outbreaks are happening due to increased rainy season, an increased severity of those rainstorms that cause an increase in cholera cases and increasing length of cholera outbreaks. So, I think, for us, ICDDRB, given its history of phage therapy, given its history of and reputation for handling cholera

cases is just really in the best position to look at clinical trials for phages for cholera.

DR. SCHOOLEY: Okay, and Dr. Boeckman has some questions for Dr. Hopkins related to the way you see the PhageBank working. Mainly, whether or not the PhageBank will have vials that are ready to pull off the shelf like an antibiotic or whether they need to be propagated in the hospital. And what kinds of concerns you have about stability of the phage stored in the hospitals or whether you'll be rotating them through and how that will work from a practical perspective?

DR. HOPKINS: Right now, we—like I said in the talk—we have these PhageBank freezers that are at minus 80, sort of liquid formulation. We do plan to get it down to refrigerated conditions in the future. Does that address the question?

DR. SCHOOLEY: Yes, it does. I mean, I think, what I'm hearing is you're working on ways to have them, essentially, be stable in the refrigerator in the pharmacy and be used

as needed, with stability testing that would determine what the rotating interval would need to be. Is that, basically, the long-term plan?

DR. HOPKINS: Yeah. I mean the hope would be that we could, you know, keep them at refrigerated—I mean the long-term plan would be refrigerated temperatures for long term. But, that being said, you know, we can continue to use minus 80 even through Phase 3 if we need to, because we have the PhageBank minus 80 freezers in place at the sites, so that's always an option, but we do want to optimize that, and there's ways to do that. It's just another effort that was going on.

DR. SCHOOLEY: And a couple of questions for Locus, related to engineering phages since that's your forte. Are there other engineering plans you have, dealing with things like biofilms, or improving stability of the phages, or improving killing efficacy? What other kinds of tricks do you have up your sleeves?

DR. OUSTEROUT: Thanks for the

question. So, we do explore all different aspects of engineering bacteriophage. CRISPR\Cas systems are quite large, so they've made us experts in being able to, basically, modify whatever we want with phage. The flip side is we all know we don't really have—you know, the phage genome, in general, is a pretty dark space. So, we spend a lot of time knocking out various genes, looking at how these things work. We certainly can knock in a variety of genes. I think the purpose always comes down to what's the benefit of doing that. For us, with the CRISPR\Cas system, it's been a way for us to have a more universal way of maximizing the bactericidal activity. We've certainly looked at how to engineer host range, we've certainly looked at how to do different factors on it. But, typically, we rely on, perhaps, automation methods to find the right phage and formulation development to make them stable.

DR. SCHOOLEY: Okay, and since you're going to do all of this manipulation, Dr. Stibitz at the FDA is worried about the

environment. What are you going to do to protect him?

DR. OUSTEROUT: In general, what we're doing is working with regulatory agencies, trying to decide what's the risk\benefit of these, and, I think, if you unpack that for each organism, how do you determine if we've introduced something that makes sense. And so, as an example, CRISPR\Cas systems are found in bacteriophage in nature, and the question is, you know, how do we inform ourselves on what's appropriate to do and what is not.

DR. SCHOOLEY: Another question here related to regulatory aspects of using engineered phages. Do you see differences from the regulatory perspective in the U.S. and outside, ex-U.S., in terms of your experience so far?

DR. OUSTEROUT: Yeah. I think that's, you know, an inevitability both for not even engineered phage, but for using phage, period. So, you know, if you're a fixed phage, if you’re magistral phage, these are all going to

have some interesting regulatory components to it. With respect to the engineering part of it, you know, what we are essentially doing is trailblazing. So, we're working with each regulatory agency, we're working on what the risk benefit is and what data needs to be driven in order to get to those answers.

DR. SCHOOLEY: Okay. So, I think, we have time for one more question before we go along to the panel discussion, to the focus sessions. This has to do with cocktails and the strategy of using them as simultaneous cocktails or sequential cocktails. Why don't we ask Dr. Hopkins and Dr. Patel, who has been seeing emergence of resistance as one of the issues in clinical trials, and Dr. Aslam, who's been using them clinically, each to give us some feedback, and others of you as well. Any thoughts about how to use them in combination?

DR. HOPKINS: My thoughts, I guess, would be number one, the testing is critical. So, knowing, you know, knowing going into the patient, or the trial, knowing what your

phage-phage interaction is, is useful. I think, you know, using more than one may be, at the end of the day, the way that we end up going forward. In our trials, we do allow for up to, you know, more than one phage. So, it's not necessarily a single patient, single phage treatment. But, you know, again, ideally, you would need to know up front if you're going to use them together, you know. Even if you're going to use them separately, it's nice to know whether there is interaction. So, that would be what I would advocate for, is to do the testing up front. Ideally, if you're not using them, you know, together, and you've tested them together, then you might want to separate them out.

DR. SCHOOLEY: Robin or Saima?

DR. REINDEL: Yeah. I mean, I can comment. I think the short answer is that we don't know the answer to the question, and we should be honest about that, right. And when look at this from an evidence-based medicine standpoint, that's your answer. Why a cocktail? Well, if you're treating empirically

and you want to have a chance of covering what you're treating, that could make sense. I don't think most phage therapy is being considered like that, but that, you know, is how we treat very sick patients with conventional antibiotics, too. But the idea of cocktailing multiple phages together that are active against what you're targeting could, perhaps, prevent with selection of resistance, perhaps. It depends also on mechanisms of selection of resistance, right. If they're all active, but they're all acting through the same receptors, etc., and the mechanism of emergence of resistance is the same, that logic may not make sense. But also, what we talked about earlier the possibility that there's a resistant subpopulation that's pre-existing, again, kind of the same thing, may make sense. We don't know the answers to these questions. So, these are important study questions for the future, in my mind.

DR. ASLAM: I just want to add one thing to that. I agree, you know, we don't know. But, anecdotally, what I've seen is, you

know, when we treat *Staph aureus* infections, we treat it with single phage and it hasn't been an issue. With *Pseudomonas*, you know, chronic biofilm infections, there are always, or almost always, you know, multiple isolates. And, I think, it makes sense, you know, if we're treating a patient, we don't want them to get worse, we use a combination of phages so that we know that those known bacteria isolates are covered. Some cocktails are formulated with known synergy between phages, so that they're actually more active together than when alone. So, I think, part of it also depends on what bacteria you're treating, you know, with what phage. There's a specific interaction as well that perhaps may, you know, determine that too.

DR. SCHOOLEY: And since we haven't heard from Dr. Reindel, what FDA issues do you see in combinations of the phages?

DR. REINDEL: Oh. I think that some of that gets to, you know, the necessary CMC information that you need to provide, you know, in a clinical development program, if

you're using a system like PhageBank or you're planning on adding phage in and out of any given system and the need to provide adequate CMC information for each phage that you plan on giving. And then, you know, everything everyone says it's true, I think, this presents a lot of research questions that need to be answered in terms of the optimal way to deliver these. And again, how do we design the studies so that we can answer those questions in a way that's going to provide us with, you know, usable data that we can use to, you know, inform treatment in a regulatory decisions. So, I think, you know, every question we're asking, you know, deserves attention and can be addressed in, you know, study design.

DR. SCHOOLEY: Very good. Thanks for the, rounding it up for us. We have had, I think, a really good discussion, about over 50 questions and got to most of them. Those of you on the panel if you can answer the ones we didn't get to, I'm sure the questioners would appreciate it. And, one question that has come

in by text from a colleague at the NIH, is whether an adaptive phage design can be found as an approach to adding phages. That gives Dr. Scott a chance to, actually, be the final word.

DR. SCOTT: Sure. It's an honor. I don't see why not. I think that kind of approach could work out. There is a class of trial designs called smart designs that look at not just one treatment arm versus another, but, potentially, treatment algorithms so, you know, trying to find the right approach for each patient through a series of steps. That could be worth looking into in a setting like that.

DR. SCHOOLEY: Okay. Thanks very much, and thanks all of you for your great talks today and for the participatory work on the panel. There's nothing worse than a panel that won't speak. So, thank you all for being so proactive and articulate. I'm going to turn this back over now to Dr. Bizzell who's going to talk to us about how to manage the breakout sessions.

DR. BIZZELL: Thank you so much, Dr. Schooley, and thanks for being an excellent moderator today. And thank you, again, to all of our speakers for their excellent presentations. Once again, we will be having our breakout sessions, and I will display on the screen the breakout sessions of today. I hope that you can see my screen. But we will be going into our breakout sessions. I'd like to thank everyone, again, for your attention today. We'll be starting those in about a minute. We'll give a little time for everyone to go in at 2:05. And, again, those links can be seen in your agenda that was sent prior to the meeting. There will be, today, the breakout sessions will focus on eCTD details, meetings with the FDA, grants through NIH, and—I'm not sure why that keeps going away—and also clinical trial designs, in detail.

So, if you would note on your agenda which session you are interested in joining and click that link. You'll be able to access that, and this main Zoom room will remain open until 2:10 p.m. for speakers to address those

questions and respond to. I'll stop sharing the screen now. And with that, I will go ahead and adjourn the general meeting and we will meet up again at this general link tomorrow morning at 10 a.m. Have a great day.

(Whereupon, at 2:06 p.m., the PROCEEDINGS were adjourned.)

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Breakout Session:

Room A: ECTD Details -- What Goes Where?:

DR. DREHER-LESNICK: Roger, do you think I should give another minute or two for folks to join or just get going?

DR. PLAUT: Maybe just one more minute, sure.

DR. DREHER-LESNICK: All right. All right. So, welcome, everybody. And thank you for joining this breakout session, which is going to cover regulatory submissions in eCTD format. And I put the “E” in parentheses primarily because the "what goes where" component of what we'll be covering today really is best described just as in the common technical document, when we discuss what goes where there. The electronic component is a separate issue, but the format remains based on the CTD. So, a brief introduction. My name is Sheila Dreher-Lesnick. I'm a regulatory coordinator in the Division of Bacterial, Parasitic, and Allergenic Products in the Office of Vaccines at CBER. So my disclaimer

slide here, the comments are an informal communication, represent my own best judgment, and do not bind or obligate the FDA.

So what I was hoping to accomplish today is really to provide an overview of the common technical document format for regulatory submissions—what it is, why it came to be, and really give you and walk you through some of the guidance documents, both the FDA guidance documents and the ICH documents, that can help you build your dossier in the CTD format. I will then go through some of the—I'll go through all of the modules, and then go through some of those subsections to see—to give you a flavor of what goes in which subsection, and then spend a little bit of time talking about how the CTD relates to the IND requirements.

The second half of my talk—it's actually less than half—I'll spend most of my time talking about the CTD format. And then I will go into some of the requirements for the electronic aspect of regulatory submissions and the resources that are available to

sponsors to submit their regulatory documents electronically. And what I want to say here is, you know, this is a breakout session. I do have slides here, but I do hope that you feel free—it's a smaller group today, so feel free to ask questions throughout, but I will also have breaks throughout the slides where I'll give everyone an opportunity to ask questions about slides that came before that, and possibly discuss a few specific concerns that you might have, or questions you might have about where to put in information that's specific to phage.

And what I also want to remind you is a lot of these resources that I'll be going over—and some of them I'll focus on more than others—are resources for you, but they're also the same resources we use at the FDA, so for training, and so it really is a two-way—it's used for both, for both reviewers in the agency but also a good resource for sponsors.

So, what is the common technical document? So, basically there was agreement across all of the ICH regions to assemble all

of the quality, safety, and efficacy information in a common format, and this will help harmonize regulatory submissions, implement good review practices, like I said, for the agencies, and also, the hope was to eliminate the need to reformat information for different regulatory authorities, and make it easier for companies to submit these documents to different regulatory authorities. And you'll see this graphic here, what they call the CTD triangle. And basically it just depicts sort of the structure of the document with module 1, and the amount of information that's really contained in each of those, with the majority of the details for each section in modules 3, 4, and 5, which represent quality, the nonclinical study reports, and the clinical study reports.

So, as I've already alluded to, the CTD is organized into five modules. Module 1 is really regional, specific to each region. And the harmonized portions of the CTD really focus on modules 2, 3, 4, and 5. And what goes into module 1, if you're submitting to the

FDA, for instance, you might want to look at specific FDA guidance for these modules. And so what I want to point out here is that the main resources that you're going to be focused on for eCTD submissions or submissions in eCTD format, is to really look at both the ICH documents that are available on the ICH website, but also then if you're submitting to the FDA, look at the FDA-specific documents, because they provide an additional level of detail that is specific for FDA submissions. And the two documents, the FDA-specific document, other than the general ones, the ones that I found most helpful for our reviewers, but also that I point sponsors to, is the comprehensive table of contents, which then provides a really precise listing of headings and hierarchy for where you could put the different parts of your document and the information in your document.

So, first to go over module 2. So, module 1 has all of the regional administrative information, and then module 2 basically provides an overview for all of the

subsequent modules and sections. And so you'll see that there is a quality summary, a nonclinical summary, and then the clinical summary. So, module 2 are basically your Cliff notes for the rest of the dossier, and really it's meant to be a high level overview, to give the reader and the reviewer the background to understand the entirety of your dossier. So, each section then should contain enough information to provide the key points for the corresponding modules. In section 2.2, for instance, you would have an introduction to your product and to your study. Section 2.3 should be an overview of module 3, 2.4, and 2.6, the overviews for module 4, and 5 and 7, the overviews for module 5. And the point I'd like to make here is that because module 2 is the summary module, it really shouldn't contain any new information that's not described in more detail or present in modules 3, 4, and 5.

So, I work in the product office. So, the module that I'm most familiar with is module 3, which covers quality or CMC

information. And the two resources that we rely on the most here is the ICH guidelines for module 3 and then of course the FDA resource to look at the specific subheadings. And I think it's also important to note that it's good to make sure you're working with the most updated version for these, because they do make tweaks over time. The ICH document has been pretty standard, but the table of contents and the sub-points in the hierarchy for FDA has undergone a few tweaks. So, it's important to make sure you're working with the most recent version of that.

So, the first part in module 3 is to really go into the details of your drug substance. And the subsections here are basically broken up into the sections listed here, which is the general information, your manufacturing process, the characterization, control of your drug substance, any reference standards or materials you might have, container closure if you store your drug substance, and then available stability data or a detailed stability plan for your drug

substance.

And again, you know, we get a lot of questions sometimes from sponsors who aren't sure where to put what information and how to incorporate it, if it doesn't exactly fit those subheadings. And we often direct them to this comprehensive table of contents. And I have an excerpt of that here. If you see on the left, and this is what I mean for the FDA-specific hierarchy, each section has even more subsections, and these are pretty standard for all of our submissions. So, if you think about where you want to put your information, you want to look at the different subheadings and see where it makes sense to put that information.

And so, I want to pause here for a few minutes to see if there are any questions that you might have about these subheadings or what information, some phage product-specific information that might not necessarily be obvious in terms of where to put, based on these headings here. Are there any questions right now?

DR. TROY: Hello, I have a question.

DR. DREHER-LESNICK: Yes, please.

DR. TROY: My name is Alice Troy. I'm with SNIPR Biome in Denmark. For the sequences of the phages, should they go in 3.1 characterization or 2.1 structure?

DR. DREHER-LESNICK: That's a really good question. So you're talking about the…

DR. TROY: The genome.

DR. DREHER-LESNICK: …of the sequence, the genome sequence and not the— right. So, I think for the genome analysis, I imagine would go into the characterization. So where you're discussing the structure and other characteristics. What was the other place you were thinking about putting that?

DR. TROY: I'm thinking of the full sequence of the genome.

DR. DREHER-LESNICK: The raw data?

DR. TROY: Yes, where would that be put?

DR. DREHER-LESNICK: That's a good question. So we have gotten, we have had instances where the raw data, the raw sequence

data was submitted outside of the CTD as a separate submission. And they're often so large that they're submitted either—in separate drives to the agency directly. So it's outside of this format, and Roger, you've had some recent experience with that. Can you add anything to the raw sequence?

DR. PLAUT: Yes, so, that's correct. If you're referring to raw sequence data, it's large and would require—be required to be submitted separately, but if you're just referring to, you know, the closed genome sequences and, you know, any annotation, that can actually be submitted as part of the CTD.

DR. DREHER-LESNICK: Right.

DR. PLAUT: As to where it should go, I think we had a discussion about that the other day, Sheila, right?

DR. DREHER-LESNICK: Mm-hmm, yeah. Yeah, it would go under characterization, and I think that would be the best place for it. And that's where the reviewers would be looking for it. Does that answer your question?

DR. TROY: Yes. I have one other, if I may.

DR. DREHER-LESNICK: Oh, please, please go ahead.

DR. TROY: Yeah. So for non-compendial raw materials, if we want to submit to supplier certificates of analysis, do we put them as images in control of materials or…

DR. DREHER-LESNICK: Yeah, yeah, I would put straight it in there, yeah.

DR. TROY: Okay. They were my two questions. Thank you.

DR. DREHER-LESNICK: Thank you. Anyone else have questions?

DR. TROY: Actually, I had one more.

DR. DREHER-LESNICK: Okay, go ahead.

DR. TROY: If you have a cocktail, I assume we should have an S for each phage? Is that a correct assumption?

DR. DREHER-LESNICK: That is, think, the preferred way to do it. And there are some—but there is some flexibility there. So if you have multiple drug substances, if the

manufacturing process is entirely the same, and all of the testing and the release specifications are all the same, there might be a way to consolidate and have it all under one 3.2.S and then write the specific characterization information for each phage under 3.2.S.3, but it really depends on the manufacturing process, but I think the preference is to have each individual drug substance have its own 3.2.S.

DR. TROY: Thank you.

DR. DREHER-LESNICK: Are there any other questions? If not, I will continue on to the drug product. So, as with section 3.2.S, section 3.2.P will cover all of the drug product information and has its own series of subheadings. The point we want to make here is to make sure that you really tease out what is characterization versus control. We sometimes see information that's put in one location when it really should be in the other. And you know, if we look again at, sort of the hierarchy and the subheadings here, you know, we want to think about what are you—if it's

really part of—the tests you're proposing, for instance, is it part of product characterization, or is it release testing information? Because if it's characterization, it will go under the characterization subheading versus the control subheading. And it's not listed here, but if you have a placebo in your study, you would need to provide the information for your placebo as well. Are there questions here about phage products at the drug product level and where to put information?

There's one note here that's specific to FDA. And it's important to look at the ICH guidances for that. So, we, in some instances, the validation of the analytical procedures are listed in here, but the actual validation studies are then in the appendix. So, there's a lot of information that I don't show here that are included in the appendices, such as the facilities information. A lot of the validation studies are also put in there. Are there any questions? Okay. And we can always come back if questions come up later.

So, again if you go into module 4, and you're looking to submit any nonclinical studies that you've done and reports of nonclinical studies, the ICH guidance really does go into a great amount of detail as to where you put what type of study. And those are then much easier for the reviewers to find. And depending again on, you know, the review division, it's good to have those separated out, because different reviewers will cover different aspects of nonclinical review. Just to give you as a sponsor sort of an insight into how we're reviewing the information, if they're in the—if they're included in sections that are not where they're meant to be or not, where we don't expect them to be, they might not be found right away. And so there could be several rounds of sort of back and forth with the sponsor to make sure the information is actually there.

And then for module 5, there are a lot of resources here. And there's a lot of detail that goes into module 5. And again, I

would definitely rely on the ICH guidance here to—for the descriptions, they really they go in great detail in each subheading describing what data need to be included in what section, and you have everything from the, you know, the PK studies to the efficacy and safety studies, and the subheadings here then for each different study would be listed under this section. Any reports of post-marketing experience would be here and then case report forms are then in 5.3.7.

So what I wanted to do, since there—it seems that there is a lot of discussion about INDs and how to file an IND, I think my FDA colleagues have already mentioned how to file an IND and that—what is admitted in an IND, and what's required to be submitted in IND is spelled out in the Code of Federal Regulations, in the CFR, and specifically CFR 312. And the content is listed in 21 CFR 312.23. So I just wanted to take a little bit of time to go over how—where to put information that's required by the CFR, and that there are resources to guide you as to

where to put them when you're submitting your document in the CTD format. So, the resource that will help you do that is the FDA resource that I note here, which is that comprehensive table of contents. And that does help—it does help navigate where to include all of the required documentation that you need as it's spelled out in the CFR. And it also provides a good overview of the different requirements and the corresponding CTD sections, and it—not only does it specify which module, it will really go down to a specific subsection in each module. And I just provide a little snapshot here, to show you, for instance, where the different forms would go, where requests would go, withdrawals of INDs, so these really are—and this module 1 will be specific to FDA since this module is very region-specific.

Before I move on to giving you an overview of sort of where the—what resources are available to you to submit electronically, do we have—are there any questions or is there anything that you'd like to discuss in terms

of what goes where in the CTD format? Has anything else come up? I can always go back to some of the other slides as needed. Not hearing anything. Nope? Okay.

And so, what I want to mention here is, again, this breakout session is meant to provide you with the resources that you need to put together your submission, the CTD format, and now the electronic submission. And so, what I'm going to spend a few minutes on is to just go over what the requirements currently are, what resources are available to you, and you know, just as a reminder, we—I'm at the receiving end of these electronic submissions, and I'm by no means a technical expert, but we do have an entire team of experts at CBER that can help you navigate all the electronic submission specifications and data standards as you're compiling your regulatory file.

So, the electronic submission requirements apply to all commercial investigational new drug applications. So, all commercial INDs need to be submitted

electronically. And this is also for all New NDAs and BLAs and any subsequent submissions to the applications. So, if you filed an IND, and you need to submit an amendment, that amendment needs to come in electronically as well. And it's not considered part of your file unless it is submitted through the electronic gateway. So, included here are also master files, as I know some of my colleagues have already mentioned and discussed, and I'll have a few bullet points on master files on the next slide too.

So, electronic submissions are not required, but we do recommend that—are not required for non-commercial INDs, but we do really recommend that sponsors submitting research INDs or large expanded access INDs, still try to submit in electronic format, and this just helps with—it helps with the lifecycle of the file and is really a good way to communicate with the FDA. The larger the dossier, the easier it is for us as reviewers to really keep track of if it's in electronic format. The—it's also optional but recommended

for submission for blood, blood components, and source plasma and promotional materials for prescription drugs.

So master files, as of May 5, 2018, were also included and are now required to be submitted electronically. So, any new master file or any amendments to existing paper master files have to now be submitted in electronic format, in the eCTD format. And I think you've already heard that master files, are really a mechanism for manufacturers to provide confidential manufacturing information for FDA review, which then can be used by other sponsors to support the use of the product in their INDs. And since master files can be very specific to CMC, you'll see that the eCTD may only contain information in certain modules. And it just will depend on the type of master file that you're submitting. And I've put a link here as a resource that will give you a little bit more information about master files, how to submit them, and what different types of master files are available.

And so, again, as you're getting ready to submit your file electronically, you know, I want to direct you to all of the resources that are available at FDA, and this really just provides an overview of the resources that are there. And if you go to the website that's listed here, you'll see each and every—you'll see a link for each and every one of these components and resources associated with them. So we have resources for you to learn about the eCTD. These are video or class modules. There are the specific documents that go along. We have FDA guidances, data standards, conformance guides, and a lot of fact sheets. So, it's really going to be important for you to look through all those resources, to make sure you understand what FDA requires.

You can then submit these fillable forms, and to learn how to submit compliant PDFs, and once you have all that, you will get in touch with the relevant center, which is CBER for phage products, and then request an application number. And they do have a

mechanism by which you can do a practice run, so to speak, and send a sample submission, once you've registered and have an account with the agency, and it's what we call the electronic submissions gateway. And that is the input for all of our electronic submissions.

And I think this goes to the question that someone raised earlier, you know, everything needs to be submitted by the electronic submission gateway, but we can only handle up to—files that are up to 10 gigs. If there are files that are larger than that, then it's really important that you contact the relevant center and get the details as to how to submit that information.

So, the guidance document that I think is the most helpful for guiding sponsors through setting up electronic submissions of regulatory documents is the following one here, and it's really pretty comprehensive. It'll go into everything about the details for the—specific to electronic submissions. It'll guide you through the different data

standards, and it will direct you to different ICH documents as well. So I think it's important to really look through this resource and then also the corresponding ICH resources, because the FDA resource is based on the ICH documents.

And this one in particular will walk you through the submission structure in terms of how granular you can get, how many subsections you can have, how to organize your files and folders, which is all based on the ICH guidance, but again is really specific to the FDA requirements as well. It will discuss how to maintain your document lifecycle, how to replace and how to remove, and how to really source and guide you through the clinical data. And they're very specific requirements. And so, it's important here that you adhere to all the technical specifications that are listed, and there's separate guidance documents that'll just go into the technical specifications for your data and the datasets in the study information. So, it's very important to go through those, and if you have

any questions to contact the technical team or the relevant review division, who can help you—who can help guide you through this process.

So, these were the two main websites that I think I want to direct you to, for all of our resources. Again because the FDA resources are based on the ICH ones, it's really good to go visit the ICH website and start with that, and then layer on top of that the FDA resources that are available. And there are a lot of different guidance documents. There are videos, there are class modules. And of course at any point in time, you can always reach out to the agency with—if you have questions about your specific file and how to get set up for electronic submissions.

And I think that's it. So I want to thank my colleagues who helped with this slide presentation and gathering the resources. So, I will go back here to see if there are any questions at this point, or if you want to discuss anything in particular about a

subsection or requirement. We do have quite a bit of time left, I think. But if there are no questions, I am happy to give you 10 minutes back.

I don't see any questions in the chat either. So, again, you know, if there are any questions as to what resources to use, definitely start here. It will take you to what you need. And then reach out to the center if you have anything that's not addressed here or doesn't make any sense. All right? If there are no more questions, I think we can be done for today.

DR. PLAUT: Thank you.

DR. DREHER-LESNICK: All right, bye.

MR. PINSON: Thank you again, Sheila. This is the AV host. That concludes our meeting for the day, and on behalf of NIAID Meet AV, I hope everyone enjoys the rest of your day. Thank you.

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Breakout Session:

Room B: Meetings With FDA - What is Expected?:

DR. STIBITZ: Hey Susan.

DR. LEHMAN: Hi. The unfortunate part of this is that I cannot share my slides and also see other people.

SPEAKER: Right now, you're sharing your main screen. If you hit share screen, you'll be able to share just your PowerPoint. Once you hit share screen, you should see the PowerPoint window pop up, and you can on that one to share.

DR. LEHMAN: It did not work yesterday.

SPEAKER: There you go. You can put it into presentation mode.

DR. LEHMAN: So, you're seeing the full…?

SPEAKER: Right now, I'm seeing PowerPoint and where you can edit. It's not in presentation mode currently.

DR. LEHMAN: Interesting. I'm going to try one more thing because it did this

yesterday as well. There's something about multiple screens. Is that better?

SPEAKER: Yes, that's way better. There you go.

DR. LEHMAN: This is a trick of multiple screens and presentation mode.

SPEAKER: Nice.

DR. LEHMAN: I'm learning new things all the time.

DR. STIBITZ: When will you need them again? OK, Susan I'll go on mute, I guess, and just wait. If you want my input just holler.

DR. LEHMAN: Feel free to speak up if the spirit moves you.

DR. STIBITZ: Fair enough.

DR. LEHMAN: I think—OK, our number of participants has been stable for a few minutes, so I think I will go ahead and start. Anyone who continues to join won't have missed too much, I don't think. The purpose of this breakout session is to talk about meetings with the FDA and what you can expect. For those—I see a lot of names, people I haven't met yet, which is great.

A little bit of my background that might be relevant to this is that before joining the FDA, I spent a number or years with a company that was developing phage therapy products, and so, I've had experience with FDA meetings, particularly pre-IND meetings from the—participating in the sponsor team and also participating in the FDA review team, and hopefully that combination of perspectives is helpful for this kind of a breakout session. As you will have become very familiar with from all of my other FDA colleagues, my comments represent my best judgement. I am endeavoring to give you accurate information, but my comments do not bind or obligate the FDA in any way.

I want to start by drawing everyone's attention to this guidance. It specifically addresses formal meetings between the FDA and sponsors. You can see at the bottom, the Center for Biologics is listed. That's actually just a useful note in general if you're looking at guidances. Make sure that the guidance lists the center that's relevant

to your product on the bottom, because that will help you have some assurance that the center that is relevant to your product has participated in drafting the guidance. If that's not there, it may have quite a bit less relevance.

The guidance is not very long. It's pretty easy to read. It describes the different meeting types, the timelines associated with each meeting type, and it also gives you a pretty good list of what to include in the meeting request when you file that request, what to include in the briefing package or the meeting package, and I'll go over what that is in a few minutes as well. There's just a lot of helpful information in there, and as I said, it's not very long and it's pretty easy to read.

There are four general types of meetings. The INTERACT meeting is a very early, informal discussion to get some initial feedback on novel issues. It's not intended to serve as an early phase meeting. It's for a sponsor who’s just kind of thinking about what

they're doing. It's intended to address really novel, specific issues that exist within a development plan.

Type A meetings are used to address an issue that's actually stalled the development program, so maybe there has been a significant safety issue that's arisen during a clinical trial. Maybe a study has been put on clinical hold, and there's some discussion needed to figure out how best to resolve that clinical hold.

The type B meetings are pre-IND meetings or end-of-phase meetings, so for example, end of Phase two before you progress your study into Phase three, and these are probably the most common types of meetings that are really relevant to people attending this meeting. I think most companies developing a phage therapy product are in this kind of stage where a type B pre-IND meeting or potentially end-of-phase meeting is most of the activity that's going on.

There are also type C meetings, and these are kind of a catchall. It's everything

else. If it's not a type A or a type B, it's a type C. Sometimes this can be used just to get a written response to a very specific question that isn't really a full pre-IND meeting. Sometimes it can be used for other kinds of conversations as well, and there are some more examples given in the guidance.

The focus of this breakout session today is really the type B pre-IND meetings for the reasons I was just describing, and specifically in context of phage products that are reviewed by CBER within the office of Vaccines.

Actually, before I get started, I want to see, can I see hands raised in the process? No. I was hoping to—can someone just try. Do you guys have the option to raise your hands and have it show up? Oh, excellent. Do me a favor and if you have any prior experience with FDA meetings, especially type B meetings, pre-IND meetings, can you just click the little raise hand button? I just want to get a sense of what people have done. I got a few hands, a few thumbs up. How many

people are looking at this as something they're likely to be doing in the near future? OK, a smattering. How many are here out of curiosity because they've never done this before and the thought terrifies them? OK, a couple of those as well [laughter]. All right, please do speak up and ask lots of questions, and we will try to make this seem like a less obscure kind of process or experience.

A typical pre-IND meeting, you submit a request, like I said, there's a detailed list of what goes into that request in the briefing package, and then after 21 days, the FDA will respond and either do a little bit of back and forth to schedule the meeting, based on the dates that you've requested and the dates that are available, or can also deny the meeting. If there's a denial, there's a specific reason. Maybe the wrong type of meeting was requested, maybe the information that was provided in the initial request was substantially insufficient in some way. If it's denied, it will be explained why. Assuming that you've requested the meeting,

you've provided the required information, it's appropriate, there will be an effort to schedule that meeting.

Thirty days after the meeting request is submitted, the meeting package or the briefing package is due, and this includes more information than was in the initial request. So, the initial request has some administrative information in it. It also asks for a list of specific questions that you'd like to discuss in your meeting. So, these are specific questions about your development plan, about your product, about your CMC, about your clinical trial, whatever it is that you want to get feedback on. So, based on those questions, the meeting scheduling incorporates things like who needs to be there to address those questions and that kind of thing, and then at that 30-day mark you submit a full briefing package.

So, now in addition to the specific questions that you're asking, you provide background information that will help the review team answer those questions, that will

put the questions in the appropriate context. For example, if you have only CMC questions, questions about your product, you still need to explain how you plan to use it. You need a little bit of clinical information, because the things that are important to your product will depend on how you intend to use your product. So, that package comes in at this 30-day mark.

And then, there are a couple of formats that a meeting can take. It can be-pre-IND meetings are typically teleconferences or written response only, and if it's a written response only, you'll get your written responses at the end of that second 30-day period. If there's going to be a teleconference, you'll get some preliminary responses a few days ahead of time and then you can request that only a subset be discussed in the telecon, and in that case, 30 days after the telecon, there's sort of a final set of minutes that FDA will send back.

Now, I've got a couple asterisks in here. COVID-19 has affected some of these

parameters. So, right now, there's—to accommodate COVID-related workloads, this time period has gotten longer. I think it's now 60 days. Is that right, Scott?

DR. STIBITZ: Yes, I think so.

DR. LEHMAN: And one of the other effects of some COVID related adjustments is that all of the pre-IND meetings right now are receiving a written response only, rather than a group teleconference; however, outside of COVID, both telecons and written responses have been options, so my plan today is to talk a little about both and address some questions about both. The rest of this, I don't have many more slides. I have a few that have some different tips and things that we can talk about, and I think I'm going to run through this first slide first, and we can have some conversation about what's on this and about what was on my previous slides, and then as the conversation progresses, we can move to some of the other two slides I have.

So, in general, perhaps one of the most important things that you can do with

your meeting package is to be sure to ask very specific questions, and then make sure that you've provided enough information for the review team to actually answer those questions. So, for example, if the question is, "Is my manufacturing plan acceptable?", that's really hard to answer. In part, it's because it's a huge question, and it's very hard to provide a specific answer to a really big question. So, try breaking it down. Present a table that has your product release criteria and ask if those release criteria are acceptable. If you have a specific assay that you're using for product release, and you want to say, "Is this assay, OK?" or "Are these acceptance criteria for this assay, OK?", now you have a very specific table that you can share in your meeting package, and you have a couple of specific question that you can ask. Those are much easier to answer.

In that example, I mentioned, you might ask whether an assay is OK to use for a particular purpose or for your stage of development. If you have that kind of

question, make sure you describe the assay. It's not enough to just say, "We're going to do PCR." What are you going to do with the PCR? What are you looking specifically for? Do you have multiple sets of primers, looking for multiple things? B, give us enough information to know whether the assay you're describing does actually answer the question that needs to be asked. It is especially important if you're talking about something that's safety-related. So, I'm going to pause there and ask for people to—you can unmute yourself and ask questions. You can turn on your video if you'd like, or you can type in chat.

DR. STIBITZ: Susan, this is Scott. I just wanted to make one really quick point, and that is often we get questions from people where they're really asking us what to do. What do you suggest for this and so? We generally don't like to answer that type of question. We're very cautious about being prescriptive with sponsors. We really like to evaluate your thoughts, not to tell you what to do.

DR. LEHMAN: I rather skipped over that bit in my bullet there didn't I?

DR. STIBITZ: I don't know. It just occurred to me, because we want to have a lot of back and forth. We encourage people to come in and discuss these things, but we're really responding to you, and as Susan pointed out, the question for an assay for example, is it suitable for its intended use. You will not find us saying, "Why don't you use this assay?" or "Why don't you use this kit?" or things like that. I don't know if that helps or not. How about some stakeholders?

SPEAKER: In the context of BLA sometimes questions around reaching an agreement sometimes can be considered a review issue in that the question can only be answered in reviewing the entire package. Maybe you could speak about that a little bit in terms of, does that same limitation come up in pre-IND meetings and what sort of things can one include in the questions or in the briefing package to avoid that limitation.

DR. LEHMAN: So, are you getting at

the kind of classic response that runs, "You've not provided enough information for us to answer this question"?

SPEAKER: I'm just thinking like, a specific acceptance criterion and the question would be, "Do you agree with our acceptance criterion limit for endotoxin?" and the response might be, "Well, that's a review issue and will depend on the totality of evidence provided in the application." Maybe that's not the best example, but I guess maybe a potency assay would be a better one.

DR. LEHMAN: So, I'm going to take my best stab at this, because I think there are a couple of pieces to that. One is that, at the pre-IND level, especially, you know, fairly early phase, talking Phase one and Phase two, it's expected that acceptance criteria will continue to be refined as a product’s development continues, and so, a lot of times the proposed acceptance criteria might be reasonable given that things are still at that sort of early exploratory stage, and a response might make some suggestions as to

things that, you know, a sponsor might want to consider as they move forward. It's not saying, "We can't answer this question" it's not saying, "You have to do X," it's just saying, "As you continue to refine this assay or this set of acceptance criteria, you may want to pay attention to issue X." One of the other components of that, actually no. Now I've lost my train of thought. What was part of the-can you repeat part of that question?

SPEAKER: I mean, I was also talking about a proposed acceptance criteria being considered a review issue that can only be commented on with the entire application package and not, you know, a meeting.

DR. LEHMAN: Sometimes it's possible to sort of partly answer a question, but obviously-sometimes there's just always going to be that factor where you can't say for sure until you see the entire IND, so an answer might take the form of, "This appears to be acceptable" or "This appears to be reasonable." Our final assessment will depend on the totality of data that is presented in

the submission and things like that, and I would say particularly at a pre-IND meeting, that answer's not necessarily a bad thing. You can still get useful information out of an answer that contains that caveat, that a review of the full submission is really necessary to answer the question. And I think that goes back to this point of "Ask a specific question" and "Ask a question about a specific proposal" because you can still have a case where you've provided enough information for the FDA team to say, "This looks reasonable. You might want to be careful of this, depending on-this might become an issue, but we can't say for sure until we read the entire submission." You can still get really useful information out of that kind of response as long as you've provided enough specifics to kind of allow that. Is that helpful?

SPEAKER: Yes, that answers my question. Thank you.

DR. STIBITZ: I'll just speak to that really briefly too. Everything Susan said is

right on the money, and you have to remember that basically we're being asked, "Is this, OK?" Without the supporting documentation, so to a large degree it's a formality. We're just saying, "Yes, it looks OK, but we're going to withhold final judgment until we see all of the supporting information." So, you know, don't take it too hard. I think the thing to look for is where we're making pretty strong suggestions because this is—the whole point of a pre-IND meeting is to try to avert clinical holds, so if we're giving advice, it's because we think that if you submitted an IND without this information or with this particular aspect, it could result in a clinical hold. I don't know if that helps either.

DR. LEHMAN: I think a little bit of addition to that would be, you don't want to try and-we try to be clear and you don't want to try and read the minds-read the words, not the minds, but sometimes the words say, "we strongly recommend," sometimes the words say, "as your development plan progresses," and if something is "we strongly recommend," pay some

attention to that because, as Scott was saying, the goal from a sponsor's perspective is to avoid a clinical hold, get information in advance that will prevent a clinical hold from stalling your program.

We have a couple of questions in the chat. One of them is, "Regarding genetically engineered phages, what should typically be addressed at each stage or meeting? The environmental assessment guideline for industry is not very clear to me on genetically engineered organisms, also is there any other issue besides environmental impact to be addressed, and examples would be appreciated."

Examples might be hard, or at least any kind of specific example might be hard for us to give. But, this is a great question. An IND should contain mention of the environmental assessment, and as a little bit of background, this is an assessment of what the environmental impact of manufacture and release of a new product might be. In most cases, there is what's called a categorical

exemption that's granted to a product that's still at the IND stage, and the general rationale behind that is that this a limited exposure, it's relatively small-scale manufacture, small-scale use, and so the environmental impact is expected to be negligible.

Typically, what happens is in an IND submission, the sponsor just requests categorical exemption on the basis of—and quotes this bit that says basically because this is an IND; however, there's always a bit of space there. I think the wording is unless it's determined that exceptional circumstances may apply or something like that, and so, if there's a particular concern presented by a particular product, an environmental assessment may be required, even though it's just the IND stage. I think this is what this question is getting at. I think it's fair to say that, simply having a genetically modified phage doesn't necessarily mean that a product won't be eligible for that categorical exemption, so it's great to present your data

if you're at all worried, share the information in your pre-IND.

In some ways I'm not sure how you would have a pre-IND meeting without explaining exactly what your phages are. Whether they're natural, whether they're engineered in some way, and if they are engineered, describing what the modifications are. I think it would be hard to submit a package with a summary of your product without including that kind of description. Then you can ask whether—you can explain why you think it doesn't present a particular environmental hazard, present some data supporting why you don't think it presents a particular hazard, and why you think it should be eligible for a categorical exemption, and then we can respond. I think, Scott, I think it's fair to say, simply being genetically modified doesn't necessarily mean that there's going to be a lot of concern about an environmental assessment.

DR. STIBITZ: Absolutely. This is a message we are constantly trying to get out

there, I think in large part because it seems to differ from some of our European colleagues, but we do not classify genetically engineered phage—we don't classify them as different. We will evaluate them based on what those changes are and what phenotypes they confer. Also, I think I heard in the question that you wanted to know what that information should be provided, and I think in a pre-IND meeting, a description of what the mutations or the alterations you're making are and how you're making them. In the IND there should be detail equivalent to materials and methods in a paper. We're going to want to double check and make sure that the resulting phage is what it's supposed to be.

DR. LEHMAN: And in the IND we ask that you submit complete closed genome sequences for each of your phages, and those sequences should include whatever modifications that you've made. It should include what the final sequence of your phage is in your product or phages if there are multiple.

Another question was, "If you have a novel device or test with phage susceptibility testing questions, but you've never had a meeting with CBER about your development program, how would you suggest engaging with CBER or CDRH? Is there an order or a preference that CBER thinks is best for sharing information?" OK, I'm going to try to break this down a little bit, because I think there are a bunch of different parts to this. If you're planning to run a clinical study, and part of the structure of your clinical study includes screening for phage sensitivity as an enrollment criterion, you can do that.

Outline it in your proposal, explain how you're going to test phage sensitivity and what your evaluation criteria are going to be. So, what is the test and what results constitute sensitive and eligible for enrollment, what results constitute insensitive and ineligible for enrollment? Whatever those outcomes are, just describe them. Describe how you're testing it and which results will permit enrollment or not. If

you're testing after the fact, same kind of idea, it's just now it's post hoc susceptibility testing. Explain the test. Explain how you're going to use the results of that test in your analysis. It can be as simple as that for, you know, earlier stage clinical trials.

I think I'm going to leave it right there and ask, Sylva, if I'm pronouncing that correctly, does that address the core part of your question, or are you really trying to get at someone developing a bigger picture diagnostic test? Bigger picture diagnostic test.

DR. STIBITZ: Let me just jump in here because I have a thought I have to share. What you're talking about is possibly a combination product. It's going to have a biological aspect and it's going to have a device aspect. I think you're question shows—it’s a good question to ask and to think about this, but I'm going to be a little bit more committal, self-serving, whatever you want to call it, and just say that we're the people

who are dealing phage. If it's phage test, the expertise on phage is really in CBER at this point, and we will always work with CDRH, the Center for Devices and Radiological Health, so if it were me, I would start with us. Does that help?

DR. LEHMAN: She said yes, that helps.

DR. STIBITZ: I think we understand why you're developing this test. I think CDRH, devices, what could be more general? They get stuff from all over the place, so I think we would be a good filter for soliciting their input.

DR. LEHMAN: I've been watching the clock, and we are hypothetically done at 2:50. I think we have a little bit of leeway because we did start perhaps a little bit later, but I want to make sure that I can provide some of the tips that are on the remaining slides. So, if you do have a telecon, which hopefully will resume in the future, you have the option, in this case, you get those preliminary responses before your scheduled meeting date, so you can

decide which questions you actually want to discuss further at the actual teleconference.

If you got written answers to half your questions, and you're completely satisfied with those answers and you think, "Great. Check." That's fine. If all of them check that box, you can email your FDA contact and say, "Thanks. We're happy with all the preliminary responses. We don't feel the need to have the teleconference," and everybody gets that hour block on their schedule back. If you have maybe two or three questions left that you still want to have further discussion on, you can let your FDA contact know that these are the only three discussions you still would like to talk about. Those kinds of options exist for the telecon format.

Assuming there are some questions that you still would want to discuss in the telecon, take some time as a team and plan who's going to lead the discussion for each of those points, and plan through what you want to say. Look at the preliminary response that you received and the question you asked, and

think a little about what was it in the preliminary response that wasn't what you were hoping for. Is it because there really is maybe something that you should be doing differently that you hadn't really thought about before? Maybe you have some questions about whether your plan to address that question would be adequate. Maybe you think the response doesn't fully appreciate your background information, in which case, review what your meeting package contained and see if maybe there was some information that wasn't fully captured.

Because then you can say, "I would like to discuss this question a little further. We appreciate points X, Y, Z. We've been thinking about it in terms of some of these other factors. Does that influence the response?" and you can have a bit of an active discussion around the point, because sometimes even the most carefully worded questions and the most carefully curated background information, there can still be scope for discussion. In that case, it really helps,

like I said, to plan ahead, who's going to lead it, what you want to say, and keep that discussion both professional but also collaborative. It doesn't have to be—this is fundamentally a conversation among people who are—who want things to succeed, so have an open conversation about what the science suggests or what you understand the issue to be and let that conversation flow and hopefully come to an agreement.

Remember if you need a moment to talk amongst yourselves or if you've asked a question and the FDA team needs a moment to talk amongst themselves, either party can put themselves on mute and take a moment to discuss, but I will say if, for example we put ourselves on mute, and you don't we can still hear you. This tip may or may not be inspired by real life experience.

DR. STIBITZ: True story.

DR. LEHMAN: Scott has few real-life experiences. In the telecon format, there's no extra presentation. You don't make a presentation beyond what was presented in the

meeting package, and also while discussion around a particular question may start to evolve a bit, and you may clarify something that you didn't include in the meeting package for space, but now is clear, should be brought up and discussed. That kind of what we'll call, "new information" should really be limited to the discussion of those questions. The FDA team comes to the meeting prepared based on what you included in your package, so if you try to bring up completely new information or completely new questions that goes beyond that scope, we're not going to be able to provide a useful answer and may simply decline to answer, in which case you can address it through a different meeting in the future or some other mechanism.

DR. STIBITZ: Right, so try and think of everything, because issues that come up on the fly or after submission of the pre-IND package, will probably not be considered.

DR. LEHMAN: I guess, part of that too is when your questions for the initial meeting request—let back up here. You have 30

days to submit the meeting package. Do not wait until you've heard whether your meeting is scheduled or denied to start writing that briefing package. In fact, start writing your meeting package before you've submitted your request. At least outlining it, because what you don't want to happen is, as Scott said, is get part way through and realize you should have asked completely different questions. You can tweak your questions a little bit in between the initial request and when you submit the meeting package, but really you want to have your questions set here, which in practice means you need to be confident in what data you're going to present as supporting information, and then this month becomes a chance to edit it and polish it and have somebody who hasn't been involved in writing it read it and make sure that fresh eyes aren't confused by the way that you've phrased something or something like that, because you really have to make sure that whatever you want to discuss is in that initial submission.

DR. STIBITZ: If I can just point out, one of the reasons why we can't just take things on the fly or why we can't have a moving target is that a pre-IND package really undergoes a very thorough review. It's essentially the first installment of your IND, and so our responses, one, they're considered after review. They're the product of meetings with a review team, and there's time for sign off by the next level and so on and so forth, so that's why, you know, it takes a little bit of time and why we can't be trying to hit a moving target.

DR. LEHMAN: There's time in that process for us to consider whether the response that we're giving to you is consistent with the response to similar questions that we've given to other sponsors. We try really hard to be consistent while also responding to the unique aspects of any one application, so we want to give you specific comments about your product, and your product may differ from someone else's, but we also want to make sure, that from a big picture

point of view, we are being consistent with the requirements for different sponsors. So that review time and that time to talk as a team helps us make sure that that's the case. In part, because there's also a fair number of people who will be involved in reviewing this. It's not always the exact same people on every pre-IND meeting, and so it takes a little bit of coordination and behind the scenes discussion to make sure that we are consistently applying expectations to everyone.

We are very short—pretty much need to wrap up at this point. Are there any last questions? There's one, a thank you for our response to the other GMO question and also asking about a guideline for GMOs in the U.S. potentially being useful for clarification in the future. Scott, is there a guideline? Is there a guidance?

DR. STIBITZ: As far as I know, this has—I don't want this to sound kind of flippant. We don't have a guideline because we don't, at least in biologics, really recognize

GMOs as being in a separate category, so we do try and make this policy, which has been articulated in this workshop and in other meetings, that we really think being genetically modified, at least in the realm of biologics, I don't want to get into Frankenfoods, etc., but at least in the realm of biologics, we don't view that as a separate thing, due to its genetic engineering, and so it's not immediately clear to me what that guideline would look like. This is a message that we try to get out there at every opportunity and, please feel free to tell your friends, but that's pretty much all I can really say.

DR. LEHMAN: To wrap up, what I'll end with is we've talked in part today about what can happen in a telecon format. Right now, we are limiting pre-IND meetings to a written response only format, which is this WRO acronym, and so the quality and the clarity of your written questions and your supporting information is even more important than it would be in a telecom. You know, no

pressure. A good clinical study synopsis and a clear target indication establish the context in which the product would be used.

Tell us what you plan to do in at least your first clinical study. Tell us what your eventual patient population will be. So, your first clinical study may not involve exactly the same patient population as your final one. Usually, you start in less ill individuals and move towards more. You may include individuals who have more severe illness in your later clinical trials as you've developed some efficacy data and have reasons to believe that more ill individuals will be helped.

But, tell us what your first study is going to look like and tell us where you're headed with it, because that information helps us ask questions about, what are the specific safety risks for your population. Your product quality, some of those things may look different depending on whether you're administering something intravenously versus orally, whether you're planning to treat a

patient population ultimately that is extremely seriously ill or are they a little healthier. Things like, that basic information, helps us answer all of the questions. Your clinical study description doesn't just help us answer the clinical questions. It really helps us answer everything.

DR. STIBITZ: I would just add that Quin Christensen has put a link to a guidance document in the chat which looks like it may be very useful, “Determining the need for and content of environmental assessments, for gene therapies, vectored vaccines, and related recombinant viral or microbial products.” So, I think that will probably be able to provide more authoritative view of the agency’s position.

DR. LEHMAN: I'm pretty sure this is the guidance that describes the usual exemption for INDs and things like that and some of the scenarios under which exceptions may occur. I saw one question about whether toxicology is required for phage products,

since it's naturally occurring. This isn't so much about it being naturally occurring, but just in general, traditional preclinical toxicology is not being required for most phage products. There's always this caveat that there could be some specific concern with a specific product that raises questions that could be answered with preclinical safely testing, but in general, classical, two-species toxicology studies are not being required.

DR. STIBITZ: The way this was stated at the workshop four years ago, after much discussion within the FDA was that GLP tox studies are not required, so it's not to say there may not be specific aspects that might be addressable in an animal model, but we don't have a requirement for tox studies.

DR. LEHMAN: I think we're going to have to end it there. We've gone a little bit over. Thank you everybody for your questions and for your time and hopefully this was helpful.

DR. STIBITZ: Bye everybody.

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Breakout Session:

Room C: Grants/SBIR/STTR:

DR. RANALLO: Hey Julio, how are you?

JULIO: Hey, Ryan.

DR. RANALLO: How does that look, Julio?

JULIO: I see your—we see the presenter view right now.

DR. RANALLO: Oh, you do. Okay. Better?

JULIO: Mmhmm.

DR. RANALLO: Okay. So, we'll get going in a couple of minutes. Till the numbers, maybe level off. Nancy, I see you're here.

DR. ERNST: Hi, Ryan.

DR. RANALLO: Hello. Thank you so much. I think we're going to get started. Just—we're a little delayed, but I want to have enough time for an open discussion. Thank you everybody for joining this breakout session. The topic, as Erica indicated, is grants, SBIRs, and STTRs. My name is Ryan

Ranallo, and I'm going to lead you through a guided discussion with my colleague, Nancy Ernst, on this topic. We thought, as a general overview, this is going to be very helpful for anybody entering into the NIH system that is not really familiar with the process, the overviews of where to find resources, and then we'll dig into SBIRs and STTRs a little bit in terms of, you know, how they differ from what I would call standard grants or investigator-initiated grants. So, again, welcome everybody. My name's Ryan Ranallo and I'm joined by my colleague, Nancy Ernst. I think you're—I'll just say you have a couple of seasoned Program Officers here to—on the line—to really answer any questions that you have on this topic, and I that think that the slides that I put together—that Nancy and I put together—will hopefully give you an overview in this process. Okay, and as Nancy said, you know, in the chat, you know, just ask questions. This is a regular Zoom, so if you want to even, you know, turn your camera on and you can also unmute yourself as well.

As far as I know, that's still possible. So, either one. So, as an overview, the NIH is a system, or a series of IC's institutes or centers, and this picture here represents the twenty-seven institutes and centers that comprise the NIH. And I'll just point out, you know, I'll do this and see if that works. No, it's not working. So, I'll point out here that NIAID is where Nancy and I are. We're Program Officers with the National Institutes of Allergies and Infectious Diseases. And just to mention here that each IC or center has its own unique mission. We—each individual organizations or centers get separate budgets. They have different priorities within that. I'll go over NIAIDs priorities. I'll talk a little bit about the dual mandate for NIAID and, you know, with respect to NIAID's, you know, how we balance our portfolios, how we targeted funding to-you know, to bolster science in a particular area. And I think the last thing I'll mention here is just, looking at this constellation of centers, I'll just mention the Center for Scientific Review here

as an extramural only. They do primarily—they do all of the review for NIH. And I'll mention that in the context of this presentation.

So, NIAID leads research to understand, treat, and prevent infectious, immunologic, and allergic diseases. This picture here was a little version—it's a different version of what Jane showed, Jane Knisely showed at the beginning of this workshop, and it's just to highlight the fact that we have three scientific divisions. The—on the left is the Division of Microbiology and Infectious Diseases. That's where Nancy and I reside. The Division of AIDS in the middle and the Division of Allergy, Immunology, and Transplantation. For the most part, with respect to this workshop and phage therapy, the vast majority of research is funded through the Division—through DMID.

As I said, our mission is really, for this meeting is really looking at infectious disease outcomes. I think it's important to remember that we do have a unique mandate. Dr. Fauci talks about it often. It's

a dual mandate to both support basic and translational research, but to also respond to emerging public health threats. I have here a list of COVID, but antimicrobial resistance has really been featured at this workshop, and I think it fits right into this category. And I put this last bullet in here just to remind everybody that both basic and applied research on bacteriophage is within NIAID's mission, and as I said, mostly from my perspective within our division, but that's not as important to know.

The vast majority—if you didn't know—the vast majority of NIH funding goes out to support extramural research. These are, more or less estimates here, in the sense that, you know, over 80 to 90 percent of the budget is spent supporting research by scientists, you know, versus other institutions, training investigators, and really communicating biomedical information. We do have intramural labs that are supported by the NIH budget, and these are of different compositions and sizes depending on the

institute and center. Sorry. Okay. I think this is where a—this is actually where I start with most investigators. Whenever I'm talking about grants is really the review process. You can't overestimate it. It's a fairly simplified view of, process, funding timelines for just a research grant in general, OK. The idea on the left is that most applications begin with both the idea and what I would consider the scientific premise, right. The preliminary research provides the basis for, you know, putting a hypothesis—proposed hypothesis in, essentially, a research plan. You know, this portion of this slide on the left is actually—and I'll get into it a little bit—where some Program Officers, you know, operate and can provide, you know, some conversations and input into your research plan. So, the timing of this is quite variable. It can be a couple of months, but if it's a, you know, a program—a long-standing program, it's ongoing. So, the application process itself within an institution, there's both the deadline we have at NIH, and then

there's oftentimes, an internal deadline because that institution's individual investigators don't submit them, but their business office or their sponsored research programs office will support and put those applications in. And so, there's actually an internal deadline, and I think it's really—don’t underestimate that need for that internal deadline, that QC, making sure you have all your documents, that everything aligns up, if you need prior approval. There's a lot to deal with, and don't overlook that internal deadline that your institution puts out there, because I think it's important. And the last thing I would say is that it oftentimes gives you—that two-week or three-week deadline gives you time to reflect a little bit and to let everything rest and to maybe come back for, you know, dotting I's and crossing T's and looking at your research plan to make sure, you know, that it's constructed appropriately.

This—our next section here, this review section, the third cartoon down—sorry,

I'm having a hard time with my—this third section down here on the review where it's highlighted—this, once it's turned in, once the application has been received—it is typically received by an institute or center. Most of the time, it's the Center for Scientific Review, but not always—if it's directly to an institute like NIAID that releases their own RFA, then they receive it directly—but ultimately, it is—a couple of things happen here. Decisions are made on what institute is the primary IC, so whenever I showed that picture of all the ICs, any one of those, depending on their mission, could be possible. And so, that primary IC is assigned, and then a secondary IC is assigned. Other things that happen during this process—during this time are, applications are reviewed individuals within the Center for Scientific Review to determine which study section is appropriate. And so, those assignments are made initially when it's received in the first month or so. Once those applications are received by a Scientific Review group, or a

study section, the process of vetting for conflicts of interest, for assigning reviewers and the actual conduct of the review, you can see, can take anywhere from, you know, two to six months. I think the review process itself—the review date—is typically held over a few days, maybe one day, but also, after that review, summary statements and the reviewers' comments are correlated and put into a published document that is a confidential document that's sent to the applicant's organization, the applicant in particular, but also, it's accessible by Program Officers, like myself, at NIAID.

Then the last thing you'll see here is a council arrow. A council review—it's a scientific advisory council, that's established through the Federal Advisory Commission Act. They provide recommendations as to whether or not the applications in bulk are acceptable for funding or meet the mandate of the mission. There's a lot that goes on during council. There's both closed sessions and open sessions. I would encourage you to

look and find and listen to as many open session council presentations as possible. And I'll get into why that's important at the end. And then the last bar at the bottom is really—it's quite variable, and it just depends on what cycle that you've submitted your grant application because it can take up to—from the time of submission to funding, depending on the time of year, can take up to a year and a half. I think I often give the answer of about nine months is about as early as you can get, but it may be a month or two earlier, but it can be extended, and I think those conversations, once you receive your summary statement, those conversations with your Program Officer will be critical, you know, to your next steps.

So, this is the timeline and the overall review process. And I think, you know, these are all on our website. I just basically grabbed some pictures and to put them in a kind of order for you. So, I think this is really important, especially with phage therapy, where the field is coalescing, as you

heard from Dr. Knisely, from Jane at the beginning, you know, there wasn't a lot of research on phage when we were back in 2015. And so, I think things like NIH reporter system shown here—so, this is just a website image on the left, and I'm going to highlight through these four bullets—just basically resources that you can use to find out information. So, the report is awesome for, you know, doing your due diligence to identify who's funded to do what. I think there's tools like Matchmaker, where you can find particular Program Officers that may hold portfolios, you can look at awards by location, but you can do some really cool, you know, investigations, if you will, into how the NIH is supporting this type of research. Prior to this presentation, I went and just looked at my portfolio through this tool and find, you know, you can really look at everything from grants to contracts to interagency agreements—you heard Jane talk about interagency agreements—on a particular topic, all of that will show up. It'll show up using this tool, and I can't overemphasize how

nice it is and how useful it is. The last thing I'll say is on the bottom of my slides, I put Google NIH report. Rather than give you, you know, the websites, I checked all these, at least from my own little perspective. I think you can get to most of these websites just by Googling it. So, you'll see that at the bottom. So that, again, is a great tool.

I mentioned council as an advisory board or advisory meeting. The NIAID council meets three times a year. One of the things that they do do is, they'll take a look at what are called Concepts. These are basically potential funding—they're early planning for potential initiatives in the form of requests for applications, program announcements, contract topics. They're scientific ideas that we would like to have our Scientific Advisor Council review. Part of what they will do is provide feedback to help shape those concepts—if they have critical feedback to help shape those Concepts. And so, just by Googling NIAID Concepts, you can get to this top panel here at the top. One of the things that I did to

make the slide deck more relevant to this workshop is to pull aspects of where we've had Concepts for phage therapy. So, if you went to this page you'd see on January 2020, DMID, our division—Division of Microbiology and Infectious Diseases—the sub-council, the sub-committee approved a Concept for improving technologies to make large-scale, high-titer phage preps. And you can see where that's listed on that page. So, again, they're early stages, there's no guarantee that they will manifest in anything particular, but it's our approach and our process. Oftentimes, they do result in a funding opportunity announcement. It's—and I'll tell you how to triangulate on what that might be and in what form, either a grant or a contract. So, as I said, council helps focus these and it's great to check these out.

This is a great landing page for finding FOAs, for finding opportunities. They have everything from, you know, contract solicitations to grant solicitations. This is again, it's simple to come across, and I'll

talk to you a little bit about, you know, how to navigate this in a slide or two. But ultimately, these are what we would call "on the street." These are FOAs that are on the street and if you talk to a Program Officer and they say "x, y, and z," they would—they may give you this link to scroll through these. So, it gives you the posting date and expiration date. And I guess my point here would be to say that don't necessarily wait for the for this. Keep your eye on—do your research, keep your eye on council concepts if that's something you're interested in doing, but this is when they hit the street and they become public. Okay, the last thing I want to do is just highlight NIAID Funding News, because if you're not signed up for this, you really should. This gives you a little bit of context. Again, I put this—I think this is the R21 FOA and I'll show you in a second on phage—but again, it's an announcement that gives you context of what we're trying to do under what FOA, what's the focus, and it gives you a heads up that these things have hit the

street. And typically, it's just an email. We all get this, and we'll look through these things as Program Officers just to see what happened, because sometimes we miss things. So, it's even important for us. And as I said, you know, it's, you know, when things go public. Okay, this, again I put this screenshot in here because, again, beyond the—you know, beyond the obvious, this grants and contracts, if you look in this blue section, you'll see all the things that I talked about and more. You'll see sample applications. It's really great advice. If you're really new to the system, you know, it's really important to scroll through all of this to understand—I'll talk a little bit about paylines and things like that, but all of these links are just really very informative. Okay, one thing I want to mention, because NIAID is a little special in that we provide, and we publish paylines. I call ourselves—I call it a payline institute. And I don't know other institutes or centers—maybe Nancy can chime in and tell me—but I don't know others that actually

publicly publish their paylines. This is a sliding scale. It really starts at the beginning of our fiscal year, and it goes to the end of our fiscal year. So, what that really means is from—I guess from the beginning of our September council to our May council, the start of our fiscal year. When we receive our budget, our budget is used to estimate what our funding levels will be, OK. We use historical knowledge as to how many grants we get in in the various different mechanisms, and we put out what are called interim paylines. These are kind of an indication of what we might be looking to fund at what particular impact score or percentile. The final paylines are almost always published—certainly, a few months ago, they were finalized. And as I said, the importance of paylines are that if your application scores at or below the published payline, there's a pretty good chance that it will be—if not a very good chance that it will get released from our budget office, and I'll call it just processed for funding. There's no

guarantee at all that if you are at or below the payline that you're going to receive funding, because there's still many steps that need to occur, but at the end of the day, you're in really good shape. Expect to receive a just in time notice or a notice from your Program Officer if your application is at or below the payline. And as I said, I think it's really helpful to know where you sit whenever you receive your summary statement and your particular—your impact score. I've highlighted here the STTR and SBIR paylines. They are at 29 for this year. I would say that would be a little bit lower. I looked at this, and they're typically in their mid-30s, maybe 33, up to 35. I have 34. I've seen 35. But the point I'm trying to make here is that the SBIR and STTRs have—and I'll make this point later in the slide deck—they use separate funds that are mandated by Congress out of the NIH budget. And so, they are—I guess I would just say that they pull from a different pool of money. And so, that's why they're a little bit—they're a little bit different than our

basic research mechanisms that we use.

Okay, I think this is really, again, thinking about how to approach grants from NIH, decoding an FOA is really critical. I put up here the FOA for phage biology that was a few years ago. And the title, which is indicated here, as Jane mentioned, I think we made a number of awards under this. It really bolstered our portfolio on phage and phage biology in general. And so, this is what it typically looks like. On the right-hand side, I've indicated a couple of different types of FOAs. There—and I didn't put it on the slide, but there's something we call "parent announcement." A parent announcement is—it's across almost all ICs and it's basically the mechanism, the FOA we use for all investigator-initiated applications, which are independent of scientific focus or other special considerations. And that's our umbrella FOAs. For the most part, they typically support R01-type mechanisms and R21-type mechanisms. The bullets here are a little bit special and I want to unpack just a little

bit about them. So, Program Announcement, also called a PA, is where we are emphasizing a particular scientific area of interest. It may be across institutes or centers, but it is a little bit different than the parent announcement in that it's—it encourages applications in a particular area. Oftentimes, the FOA is active for multiple years over multiple council rounds. And the next bullet, which is called a PAS, is just a program announcement with set-aside funds. So, the difference between a standard PA and a PAS is that they—that we have dedicated or programmed funding levels for a particular scientific area, OK. And that's important to know because it's just important to know how big the program is going to be, to maybe estimate how many awards would be made under that, and to some extent, whether or not the institute or center is really serious about funding the research. They would certainly have funding set aside. PARs are just a program announcement with a special receipt, referral, and review dates. Again, it's a little bit

different in that we have contained some aspects of the program in terms of the number of receipts. Maybe we have two. Maybe we have one. And the review process is a little bit different, and I'll talk to you a little bit about that in the next slide. And then the last one is an RFA. It's a request for applications, and this is typically reserved for well-defined programmatic objectives. Oftentimes, if not always, there are set-aside funds. You know, the mechanism is going to be quite variable and really chosen based on the program attributes that you're looking to support. So, typically we, you know, we'll look at maybe concepts. You'll look at whether or not it's going to be a PAS, a PAR, or an RFA. At the time of a concept, the Program Officer won't be able to tell you that, but there's a little bit of reading between the tea leaves on that, and you can certainly expect that the level of funding for an RFA is going to be commensurate with the size of the program that we'd like to support.

Okay, so, I think again, unpacking

FOAs—what are they? There's a lot of information. They're very long, and I think zooming in on a couple of parts—so, certainly knowing, showing here, whether or not it's a RFA, PA, PAS, is looking at key dates. In this upper section here, you'll look at the activity code, you'll look at—and again, in this overview—you'll look at whether or not, how much money is set aside for award information in section two—that type of information. Section one is where it's going to have a full description of the program, the examples of the type of research, the examples of the type of programs that are going to be supported under it. So, that is where the meat is, in section one. Looking at, you know, what type of scientific area we're looking to support. Section four and section five are really important for a couple of reasons. One—oftentimes, we're defining, you know, what type of information is accessible or—sorry—what is permissible. And what we would like to see, because defining that is really important to help reviewers review the applications that

will eventually be reviewing these applications, so the review information in section five will basically, most of it is pretty standard language, but then you'll see FOA-specific language in there. And that's really important to—remember that you're addressing the FOA-specific language, because reviewers will be looking at that and saying whether or not you are meeting that requirement. And then the last section is agency contacts. I can't over emphasize this enough. Reach out to the agency contact. Most of the time, it's a scientific point of contact. If there are multiple ICs, there will be multiple scientific points of contact, but reach out to them. They know it's coming. They've agreed to be listed on these, and they will give you as much information, if they don't have the programmatic-specific information for a particular disease, they will put you in touch with that Program Officer. So, that's—those are the key things whenever you're looking at a FOA. That's what to pay attention to. I'm sure there's other

aspects that maybe I'm glossing over, but certainly those are the highlights.

Okay, so, I'm going to transition a little bit. I wanted to—I think this is important given the nature of phage therapy and even in this workshop—to talk a little bit about the SBIR program and STTR program and the differences. As I said, they are typically—they are funded through separate funding allocations that are mandated, set-aside programs mandated by Congress. They're meant—both programs are meant to support research and development for small businesses. The two listed here that we're going to talk about are the Small Business Innovation Research Program, SBIR, and the Small Business Technology Transfer Program. They're slightly different and I'll talk a little bit about those differences. And then the last thing on the bullets here—now I'm not providing absolute numbers—the percentages there are the percentages of the total NIH budget that are dedicated for the SBIR programs. Just make sure—right, okay.

So, the one thing—I'll come back to this, and I didn't put the slide in there—I can talk a little bit about it. But small businesses have a very specific definition, you know, less than 500 people. They're greater than 50 percent owned. I think one of the most important things about the SBIR and STTR programs is that they're really, as I said, there to support U.S. businesses. Foreign involvement is, in some cases, acceptable, but I would say very rarely. And it has to be well justified. So, I think there are some things that you come across where you have multinational corporations, where maybe you're doing customized antibodies or customized chemicals. And there's only one entity in the world that can make that. There are those rare exceptions. But the reality is, if you do propose a foreign involvement, a non-U.S. based involvement, it has to be well justified. And my advice would actually be to talk to your Program Officer prior to even structuring your program that way, because I've had programs of grants that have come in

and where it's really been unfortunate that it hasn't met that threshold of being acceptable. And it really can throw a wrench into your program.

Okay, the difference between these, as I said, they're both there to support U.S.-based small businesses. I'll just, on the top SBIR versus STTRs, the PI for a SBIR must be employed by the small business at the time of award for the duration of that project. Whereas STTRs may be employed by either a small business or a research institution. So, that gives you a little bit more flexibility, as well as the commitment of at least 10 percent to the project. So, your research partners for SBIRs, you can always have research partners, but there's no mandate on the research partners except for the fact that you have to have a percentage of the small business must be receiving and doing the work on its own. You can't have—be seen as a pass-through organization that's basically contracting out the vast majority of those, of the work. And so, there's minimal thresholds

that are indicated here. For STTR, the research partners, again, are—requires partnering with a U.S. research institution, okay, and that can be a little bit more flexible in that sense. And as I said, you know, the goal is to support small businesses, and the awards are always made to the small business. But they have a little bit of different—a little bit of different flavors. And I would say just orientation, if you will, when it comes to who's managing and running the projects.

Okay, this is always a real important question that I get when talking about SBIRs and STTRs. So, the top bullet here is looking at direct costs, indirect costs, basically total costs, and the caps for these programs. I'll talk about which each mechanism is intended to support. But suffice to say, that they're fairly limited for phase one, and much more support can be given on a phase two award. These are statutory limits, okay, but NIH has a—we have asked and received—routinely received a waiver from the Small Business

Association, and it's authorized by statute that we can award grants above these thresholds. And I've indicated those thresholds in bold here. So, for NIAID, we have waiver topics and I'll talk—I think I have—I'm pretty sure I have where to find the waiver topics. But they are intended to support high-priority areas within NIAID's mission, okay? And I think the most important thing here is it doesn't require prior approval, okay? But I would have that conversation with your Program Officer just to make sure you're looking at the same thing, and that your assumption about a particular area of interest is covered by a waiver topic. But it's not something a Program officer will allow—will give you. They don't give you prior approval. That's not what happens. The acceptance under the waiver topic is made at the time of the award. And I don't think it's—sky's the limit. I mean, really and truly. You have to have a well justified budget and it's got to be—it has to be guided by the science and consistent with the work proposed. That's

a standard line for all grant proposals is that the scope has to match the budget. And if it doesn't, I think, you know, the reviewers generally let you know. So, as I said, there's phase one and phase two. Both the SBIR and STTR program have most of these components, with a few exceptions. So, early phase—this is where the proof-of-concept studies—these are phase one. They're relatively small money. It's basically looking at technical merit, feasibility, as I said, proof of concept. That is followed by a phase two application. So, if you're successful in both getting a phase one and executing the proposed aims, and you have results that would support a phase two, the applicant, again, the grantee, can apply for a phase two. This is typically supporting more, obviously, more costly studies. But basically, for translational science, it would support maybe aspects of product formulation, for product manufacturing characteristics, things like that. If it's a, maybe it's a—toxicity studies that are very costly. So, the phase two development work can really be quire

variable and it should be tailored to, you know, the project. And I would say that phase—both when you apply for phase two—it's actually considered—and you're successful—it's actually considered a renewal of the phase one. So there, they maintain the—it's called, in our language, it's called the type two and it maintains the same grant number. So, there are other things listed on this slide, like on the top, the direct to phase two, that is meant to allow for applicants who have not had prior SBIR support, who have maybe done it on their own company's funds, and feel like they can go right into the development phase.

And then there's also a fast-track application. These are different, you know, different ways to minimize the impact of having kind of a phase one followed by a lag, and phase two. The fast-track applications combine both phase one and phase two, and there's a single review that happens. The summary statement is written for the entire program. And then once the phase one is done, the progress report is turned into NIH or

NIAID, an administrative review is done. And then if it's acceptable, it moves on to phase two without an external review. So, it minimizes the delay. On the bottom here, phase two B is actually meant for further development. It's actually a continuation of phase two, as I said before, from phase one to phase two to phase two B, it is just, you know, it's follow-on R&D funding for—when you're looking for a very long development time, you're looking for FDA approval, and things like that. That is where you're really in advanced development. And the last thing I'll mention here—I won't mention the phase three commercialization because it's beyond the scope of what we would—we're going to be talking about because it's not that, you know, it's not a grant mechanism, per se. This—the CRP is the readiness—Commercialization Readiness Program. And this is a program that you can get that runs, that can be parallel to your existing awards and phase two. They're meant to provide additional funding for IND submissions, regulatory research services, and

market research, IP protection. They're adjunctive funds for your overall program, and they can be quite valuable in that regard.

So that, right. I have two more slides and then we'll open it up. And I wanted to point this out. This is just a snapshot of our SBIR. If you just Google NIAID SBIR, this is our landing page. And as I said, there—the hyperlinks here indicated towards the lower third of this image, both the NIAID's business grant opportunities. You can see on the left, it basically takes you to all of our SBIR FOAs, including contract topics. The NIH SBIR, STTR funding gives you that the higher order above NIAID. It's quite helpful. And it gets you to this link that I'll show you in the next slide.

And then the last thing—you really don't want to overlook these contract solicitations, although they're not grants and not really within our focus of this breakout session, they're very structured funding opportunities that can provide similar, you know, identical levels, the phase one and

phase two. But instead of a grant, they're a contract, and they go through that same process of concept, approval, and they should be available as you do your research. So, a great, great site to check out. As I said, if you click on that middle link, one of the things you can come up with is—and I just opened this. I just pasted this in there last night—is the FY22 SBIR contract application. This is the document on the NIH website that you can get to through that middle link. And what it does is it, along with the SBA approval waiver topics on that same site, you can get a list of all of our contract topics. And they're broken down by scientific division, particularly within an IC and then within individual extramural division. And that is, again, a wealth of information as you do your research.

So, with that, I don't have any more slides. I think I'm happy to take any questions. As I said, I'll start with these in the chat, okay? And then if you want to, based on anything I've said, Nancy and I are, you

know, more than happy to answer your questions. Okay, so Nancy, do you want us—do you want to add anything? Do you want to maybe go back? Or what would you like to do on this?

DR. ERNST: So, whichever you want, Ryan. I mean, I could take a first stab at them and then you can add in what you want, or vice versa. I'm happy either way you want to go.

DR. RANALLO: Please, let's do that.

DR. ERNST: Okay. So, since you've been talking for a while, why don't I take a stab at these few questions, and then if, you know, you want to clarify or anything, I think you have the capability of unmuting yourselves, and you can then, you know, ask any more questions.

So, the first question we have is, "Are there other centers, such as NIDDK or NHLBI that are open to phage studies?" And so, I can—I'm sure you appreciate that probably NIAID is probably the primary IC that would handle phage studies for infectious bacteria, both the basic, as well as more translational

studies. But once you start to think about pneumonia or urinary tract infections, you can imagine there's these gray areas and regions of overlap. And so, while I can't speak for the other institutes, I do think it's important for you to keep them in your mind to contact them to see where they stand on such studies. Ryan also showed you the Reporter link early in his presentation that would be good for you to search out different types of phage studies and see which institutes support them. And so, there's potential. I can't say I know specifically of any. I know that NIGMS supports more basic phage studies. But if you're thinking more about infectious disease, NIAID is going to be the primary institute, but I wouldn't rule out the others. Ryan, do you have anything more that you'd like to add to that?

DR. RANALLO: Just going back to my—what I had said initially. During that process, the primary IC assignment is where that decision—I would say, if you're soliciting—if you're applying under our parent

announcement, and it goes through the standard process, that IC assignment can be made to NIDDK or NHLBI depending on your—I would call it your indication. So, if there's more of a disease state that's, again, thinking about the Venn diagrams of NIH ICs, it's more on the side of NIDDK, absolutely. One of the things that I did do, is looked at NIH Reporter for my program. And I—while, you know, we have the overwhelmingly majority of applications for the program that I manage, there are applications that are funded throughout the ICs. So, they're there. They're just not as large of a footprint. And the last thing I would say is, there is—there always can be some back and forth on primary IC assignment. And it is important to know that. If there's any question about that, real people, like Nancy and I, answer those questions. I mean, we say, "Yes. That's something we're going to support or not." So, you can—I think you can appreciate that it's not just, you know, it's not a robot making that decision. It's real people. And if prior conversations—I don't

think I mentioned this—but if a prior conversation is impactful enough for a Program Officer to look at that and say, "Oh yeah, right, x, y, and z." So, that can happen also, as well. So, the answer's yes. It just depends on what you're looking to support.

DR. ERNST: Good. So, our second question is, "Is NIAID open to support phage research in Africa?" And so, as Ryan pointed out, we have these parent announcements for our bread-and-butter type mechanisms, R01s, R21s, and those are open to applications from foreign organizations. As he did mention, these small business programs—the grants, SBIRs and the STTRs—are focused on U.S.-based small businesses. And so, in that way, those probably would not be eligible. You'll also find that if we have other announcements—PAS, PAR, or RFAs that come out—you'll have to read those individual announcements. But oftentimes, they can be open to applications from foreign organizations. It's also, oftentimes, we receive applications from a U.S.-based organization that have what we call

a foreign component in them. So, that's a collaboration. These are usually—these can be very successful—is when there is a collaboration between a domestic or U.S.-based organization with a foreign organization. Even though the application comes in through the U.S. organization, a foreign component can collaborate with them. So, there are opportunities. I don't know what stage of phage research you're looking at, so it's a little hard to tailor that question, but there are opportunities. You just have to look through them to know. And again, I think if you need help on that, talking to a Program Officer can be very helpful. Anything to add there, Ryan?

DR. RANALLO: Only that there is—it may not be relevant for phage research, but it could be—is that we do issue other ways that are specifically designed for non-U.S. Based research programs. They're a little bit—not a little bit—they’re more infrequent, but nonetheless, they show up on our concepts. They show up in our processes. So, it'll be

there. Nothing rules it out. It's possible. And as Nancy articulated, I think, you know, talking to your Program Officer, trying to understand in that early stage where you're getting your premise and your—just your overall structure—would be really helpful to talk to a Program Officer. But it's more than possible to even support clinical trials in non-U.S. based locations.

DR. ERNST: That's right. I meant to mention that, so thanks. All right, our third question: "Is there any funding opportunity for bacteriophage-based vaccine development?" I can't think of—no specific funding announcement that is out right now other than the one I know that Ryan highlighted in the beginning of his slides. Ryan, do you have any information on that?

DR. RANALLO: I don't. I think—I was thinking about this. I don't think it should be even thought of as being, maybe, specialized. I think of—meaning it seems to me that you're—it falls into this larger vaccine focus that we have. You know, Nancy, to me, it

seems like—and we really do talk about it---- you know, without looking at what you're trying to protect against, it's almost something that—it's not that we don't target it, because it's a large majority of the research that we support—is basically vaccine development. So, I think, you know, I think having it be bacteriophage-based wouldn't—would be highly innovative, but certainly not something being targeted through an FOA or something specific. So, yeah.

DR. ERNST: So, just basic vaccine—anything that would apply to a vaccine mechanism—is likely to apply. There's nothing very specific like an announcement for a bacteriophage-based vaccine, but you're certainly open to the other vaccine-type of mechanisms or announcements that come out, I would imagine.

DR. RANALLO: Right. Yes. Yes.

DR. ERNST: Anyone else? You know, feel free to just unmute yourselves and ask a question if you like.

DR. RANALLO: And it doesn't have to

be something that Nancy and I talked about if you just have a burning question.

DR. ERNST: It could be something else.

DR. RANALLO: Yeah, absolutely.

DR. ERNST: It's very quiet.

DR. RANALLO: We're on the clock. (Laughter). We're not going anywhere.

DR. ERNST: Maybe that's it. You know --

MS. NAGEL: Sorry, this is Tobi Nagel from Phages for Global Health.

DR. RANALLO: Hey, Tobi.

MS. NAGEL: We have sometime wondered if we could apply for a scientific workshop or meeting grant in collaboration with a U.S.-based organization, ISVM, Society of Viruses and Microbes, but hold the workshop in a developing country, in Africa or Asia.

DR. ERNST: So, you're talking about an R13 conference grant, yes?

MS. NAGEL: Sounds right, yep.

DR. ERNST: I wish I could say I was completely up to date with the details of

R13s. It's been a number of years for me. I think it's possible. I know we do support conference grants that take place in other countries. I think what's going to be important for something like that, is a really strong scientific justification for that. I can point you to the person to talk to about that. If you want to send me an email—you have my name—Nancy.ernst@nih.gov—I could send you the contact information. Ryan?

MS. NAGEL: Thank you.

DR. RANALLO: Yeah, Tobi. It just highlights the fact that, sometimes, you know—I didn't go over the mechanisms of—the various mechanisms—but one of the things that happens is that conference—the mechanisms that support conference grants are managed by different Program Officers—a different officed in general. So, as Nancy said, we don't have those, but they go through the same process. I would say that they are not likely to be in, you know, that concept approval. They're basically going to be unspecified or—yeah, I would say unspecified. So, to say that it

would support that type of meeting, I don't see why it wouldn't. I really don't. I think as Nancy said, I'm quite certain it's happened in the past. And just reach out to either Nancy or I, and we'll provide you the name of the person that actually can get that specific information and confirm, for sure.

MS. NAGEL: Thank you.

DR. RANALLO: Absolutely.

DR. ERNST: Thanks for speaking up. Anyone else? We're almost at time, I think. I don't know how long we go.

DR. RANALLO: I think we're—I'm going to check. 3:05p.m., maybe?

DR. ERNST: Yeah.

DR. RANALLO: Oh, okay. Yeah, so we're done. It's supposed to be done at 2:50 p.m. We're here though, so if anybody has any one last question, otherwise I'm going to maybe get Julio to close it down. We'll give—I'll give a long, uncomfortable pause and then if anybody wants to speak up, we're happy to answer any questions.

DR. ERNST: Feel free to follow up

with us if needed after.

DR. RANALLO: Absolutely.

DR. ERNST: I couldn't handle the long pause, I guess.

(Laughter)

DR. RANALLO: I couldn't either.

DR. ERNST: It's hard for me. (Laughter). Thanks.

DR. RANALLO: Okay, everybody. Julio, we're done. We appreciate your support, for sure. Thank you, everybody, for listening and for participating in this meeting. It's been great. Thanks so much. Bye.

DR. ERNST: Bye.

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Breakout Session:

Room D: Clinical Trial Design - Details:

DR. REINDEL: I am going to rearrange and I'm going to share my screen. Okay, is that the correct view for everyone or are you guys seeing the presenter view?

DR. KNISELY: Yeah, we're seeing the presenter view.

DR. REINDEL: Okay. I just swapped it. I can't figure out --

SPEAKER: There we go.

DR. REINDEL: Okay. Okay, so, let's see here. All right, great. So, welcome, everyone. Like I said in my discussion earlier, I'm going to spend the majority of this time really discussing some of the slides that were already presented, but going into a little bit more detail, and also offering the opportunity for, you know, group discussion, questions, feedback from participants on ideas about clinical trial design. And also, John Scott is also in this breakout session and can provide me some statistical backup. So, I may

be calling on him if people have complex statistical questions that he'll be far more qualified to answer.

So, I just need to reiterate my comments are informal and represent my own best judgment as a medical officer, and that anything I present or say here doesn't bind or obligate the FDA.

So, you know, I went through all of these a little bit earlier, so I'm going to sort of focus in here, you know, on late-phase study design considerations and just spend a few minutes going into a little bit more detail on this information. And then really open it up for more sort of roundtable-type discussion if people feel like that would be helpful to them.

So, I think that when we are talking about late-phase study design considerations, you know, late-phase studies really focus on safety, always safety, but really how you're going to demonstrate efficacy of your product to support potential licensure. And once you've gotten to that point, you can decide,

you know, how are you going to be providing your therapy? And I think there are specific design considerations that go along with providing that therapy, a standalone versus adjunctive therapy in addition to antibiotics.

So, when you're talking about using bacteriophage as standalone therapy, one of the things that you really want to think about is the selection of your comparator group, and we'll get to a little more detail on that shortly. And really, if you're going to use it as standalone therapy, depending on the severity of illness of the patient, the type of infection, there do need to be some data to support the effectiveness of the product so that you can be sure that the standard of care in terms of providing some treatment for the infection is being met. There's also the question of if you use it as standalone therapy in your study, you know, what the role is for standard of care antibiotics and the timing of that as well.

The other issue that needs to be addressed and was just briefly discussed in

our panel discussion is how you approach the development of resistance and any risk mitigation strategies that you have in your study to provide rescue therapy for people who have worsening of their clinical condition while on your study.

And then, in addition, when you're thinking about bacteriophage as adjunctive therapy, there's the question of selection of standard of care for management of the infection provided to the study groups. And some thoughts about this are, you know, what is standard of care? And that may vary. One thought is, for example, management of burn wounds may vary by burn center to burn center, and, therefore, you know, the impact of variability in that standard of care may impact findings in a multi-center study, so how your study might address some of that standard of care if it's being provided adjunctive with your bacteriophage.

So, other is variability in terms of standard of care antibiotics. For example, in a study with multidrug-resistant organisms, if

there is a lot of variability in the type of antibiotics that would be provided based on the natural variability and the susceptibility patterns of the clinical infections, that's something to consider as well.

How do you interpret your preliminary evidence of effectiveness in the context of concomitant antibiotic use? And that can be addressed, you know, through study design and using different methods to approach your study design, so that you can be sure that what you're measuring really demonstrates the impact of your bacteriophage as an adjunctive therapy.

And then there's always the question of how you interpret safety data in the context of confounders of concomitantly administered antibiotics. So, one example is the hypersensitivity reaction and deciding whether that hypersensitivity reaction could be due to any concomitantly administered therapies or to your study product. So it does introduce some confounders that need to be considered.

DR. FIORE: Hey, Becca, do you mind pulling your header for your Zoom off your screen? Is that possible? Because it's taking up the title of your slides.

DR. REINDEL: Ah.

ERIC: So, Rebecca, this is Eric. If you could go to "More" to your right, and you should see "Hide"–there you go.

DR. REINDEL: Ah, sorry. Thank you for pointing that out to me, Cara. I appreciate that. Okay. So I just moved everything around. Okay, sorry.

So, okay. So, select late-phase study design considerations. So, really what you want to do for your population is think about how the subjects in your confirmatory trials should closely mirror your target population. So, you want to make sure that what's going to be in your label is the patient population that you're studying and that you've accounted for that in the way you're designing—sorry about that—in the way you've designed your study.

And so I mentioned in my talk, you

know, study endpoints. I really can't overemphasize the importance of your study endpoints, and they're really the key in late-phase development. And you have to come up with clinical endpoints that directly measure how a person functions, feels, or survives, and that can be plus or minus microbiologic endpoints. For example, for UTI, it could be measurement in the urine of colony counts, as discussed in the FDA guidance on treatments for a urinary tract infections. So, there are a lot of considerations that go into clinical endpoints, and you can discuss this with us, you know, all along the course of your clinical development program, in the pre-IND stage, at end of phase two, and we can come to an agreement on appropriate clinical endpoints for your study, but this is really important and something that deserves quite a bit of attention.

And really, you want to make sure that the primary variable can provide a valid and reliable measure of some clinically relevant and important treatment benefit in

the patient population described by the inclusion and exclusion criteria. And that seems very straightforward and sort of obvious, but I think, you know, you need to make sure that your study design really addresses all of the subtle nuance therein, in terms of what's clinically relevant, what's important, who is your patient population, who are you excluding from your patient population, and ultimately, whether or not those exclusions need to be reflected in the labeling.

Additionally, you need to design your clinical study to avoid bias. And so, the classic ways of doing this, you know, randomization, blinding, and there are a lot of different approaches to blinding that may be appropriate for your clinical trial design. I think the gold standard is double-blinded, placebo-controlled, randomized study, but obviously not all of those factors are appropriate for every type of study, which leads me to sort of the choice of comparator groups. So, a placebo study, clearly in people

with active infections, we can't not treat people, so the use of a placebo needs to be thought of in the context of, you know, providing standard of care, any ethical considerations in terms of making sure that people are adequately treated at all times, you know. And also, you know, what's the comparator, in terms of—if you're using add-on therapy, a placebo may be more appropriate, because you can do standard of care plus placebo compared to standard of care plus your product.

There can be no treatment, dose-response, active control, external control, and historical control, multiple controls, so there are a number of different approaches that may or may not be appropriate given your particular study and considerations and your product. And there are two guidances here. There's the ICH guidance on statistics and clinical trials and also the ICH guidance on controls that I think is really helpful to consult as you're thinking about how you're going to design your clinical studies.

There's also multiple types of design configurations. A parallel study, which I think is a common approach, to have two study groups that are dosed simultaneously. There's also crossover study design, where, you know, treatment is provided to everybody in the group, but there is an interim period between the groups, so that you can compare. The type of comparison that you're going to do. So, for an add-on therapy, typically you would look at superiority. Does your treatment, added on to the standard of care, result in a clinical endpoint difference that's measurable and meets your success criteria, which I'll discuss in a second? But there are also non-inferiority studies that could be considered, especially in the context of standalone therapy. And then there are also some more complex statistical trial designs that I'll defer to John if people have questions in terms of nested superiority and non-inferiority studies that can be used to answer multiple questions within the one study design.

And then some very general statistical considerations, because I'm not a statistician, and I can't say that enough, but, you know, sample size. How big does your study need to be so that you can demonstrate treatment effect? What are your success criteria? And I think that's really important to have. Be thinking ahead of time, for your pivotal or registrational studies that you're designing to support licensure, what are the statistical criteria that you need to meet to demonstrate this clinically relevant and important treatment benefit? So again, that can be discussed with us and agreed upon.

And then lastly, the other important consideration, you know, your analysis set. So, which populations within your study will you be using to assess your clinical outcome? Will you be looking at per-protocol, or intention to treat, or modified intention to treat? So, these are all areas where having the guidance of an experienced biostatistician to help you analyze the correct group based on your particular clinical study design and your

particular clinical endpoint. So, and again, all of this needs to be considered in the context of the indication you're going for. So that's the sun again around which all of these questions sort of orbit in terms of deciding how you're going to approach your study design.

And I think that was sort of—I can talk a little bit more about some of these pathways and expedited programs, etc., but I wanted to pause and open it up, because I thought these breakout sessions really lend themselves well to, you know, a smaller-scale discussion. So I just really wanted to pause briefly. I wanted to give Dr. Scott an opportunity to add or correct anything for the record that I said, and then we can open it up.

Dr. Scott, I think you're on mute.

DR. SCOTT: Thank you. I was double muted. I think you did a great job, no corrections or anything. The only thing I would add on one of those last points about analysis sets, ITT, intent to treat versus

per-protocol, and so on, FDA has been encouraging the use of a framework for addressing those questions called the estimand framework, where instead of focusing on what you analyze, the focus first is on what are the scientific questions? And then if you sort of look at that in the right way, the appropriate way to analyze it should kind of fall out of conversations based on the underlying scientific question. So there's a guidance document on that question. It's called ICH E9(R1), which is a lot of letters. But, yeah, that's all I wanted to add.

DR. REINDEL: So, is—everyone, can—is like, ready to design their late-phase clinical trials, no questions, no comments or anything from anyone? If people don't want to discuss, I can certainly spend a little bit more time on some aspects of my talk in terms of clinical development or additional information on early-phase clinical trials.

SPEAKER: I have a question about crossover design. How do you envision a crossover design using phage on top of

antibiotic background? I mean, how—you've only got a limited time, right, to treat a patient before they get better. You know, let's call it 14 days. What do you do? Seven days of one and seven days of the other? I mean, I'm interested in your thoughts on that.

DR. REINDEL: Right, so I think about crossover study design, you know, in the context of perhaps, you know, more chronic infections or colonizations. So, you could provide standard of care for a certain amount of time and then add phage onto standard of care later, so that everybody in the study gets the phage treatment, but they may get standard of care first.

SPEAKER: Okay, more of the chronic population.

DR. REINDEL: Correct. I mean, you're absolutely right in the context of, you know, an acute, serious infection, that would not lend itself well to that type of study design. And again, that's why, you know, it's really hard to sort of do a 20-minute talk or a breakout session on clinical trial design,

especially for something as complex as bacteriophage, because so much of this is going to be relevant to your specific patient population, you know, the disease process you're treating, the pernicity or the acuity of the infection, the available treatment modalities, etc. So, so much of this, it's hard to sort of lay out in front of everyone and say, this applies to every study or this doesn't. So it's a bit of a challenge to present this in a way that's helpful to everybody and—but, you know, the idea was to give everybody a sense of the variety of study designs that are available and how they may or may not be applicable for use in a specific context.

SPEAKER: Okay.

SPEAKER: Yeah, hi.

SPEAKER: Because—go ahead. Never mind.

SPEAKER: No, go ahead, go ahead. I'm just—okay, so I have a question. I mean, I never did a phage clinical trial, but just in case, in terms of how FDA sees in terms of the

statistical significance. So if data have shown, let's say there are improvement, let's say in certain clinical symptoms and certainly patients get better, but then when you do statistical analysis it could be due to the sample size of others because doing this type of study, you know, it's really selective and it depends on your product. It could be just for one type of a bacterial infection and then has to be—the bacteria had to be susceptible to the phage, blah, blah, blah, right? So how do you see that when that data come to FDA? How do you see if it has to be statistically significant or you can just show that there are improvements compared to the standard of care? But then it's not statistically significant.

DR. REINDEL: Well, I can also defer to Dr. Scott if he has, you know, some additional insight on this, but I think, you know, deciding what your success criteria are, so, things could be statistically significant, but not necessarily clinically significant. And so, I think coming to an agreement about

where FDA is with what you proposed for your pre-specified success criteria. So, say—I'm just going to make up an example here. If we say we think that if we demonstrate that, you know, the lower bound of a 95 percent confidence interval and the difference of outcomes is 10 percent, you know, we would consider that to be a clinically significant success criterion. Again, I'm just making this up for any given indication, that we could come to some agreement on that. And the rationale for any given statistical success criterion is really going to depend, again, on the nature of the illness, the study design, etc. And I'll pause to let Dr. Scott add anything here.

DR. SCOTT: Yeah. No, I agree with that. I would say in general we do rely on statistical significance testing as one of the tools we use to evaluate not necessarily how effective something is, but how convinced we are that what you saw in the trial we would see again if you did another trial or, more specifically, we would see it in the

population if the product were licensed. It's one component of what we usually look at for establishing substantial evidence of effectiveness.

It does depend on the specific situation, so, there are some settings, disease settings, where there are no alternative therapies, and the natural history is very dire and well established, where it might be possible to show a positive treatment effect from very few patients, because we know for sure what's going to happen to them absent the treatment. But that's not typically the case in infectious disease, where there's, I think, just often too much variability in outcome to really know what's going to happen to any one patient absent treatment.

DR. REINDEL: Thanks.

DR. FIORE: Becca, you have several questions in the chat, I'm not sure if you can see them or not?

DR. REINDEL: Yeah, thank you, Cara. So I'll just read this from Samuel Penziner—I hope I'm pronouncing that correctly. It has

been well established that the design of most phage trials thus far have been suboptimal. What do you think are the main areas that should be improved/addressed in the design of future trials?

Well, I guess it depends—that's the stance answer, right? You always say, the answer is it depends. But I think it depends on why the design has been suboptimal. And so I think, you know, with the PhagoBurn study, there was some concern that the outcome—you know, that the study outcome wasn't as successful as they had hoped because they had some CMC issues in terms of, you know, I think—and any of the microbiologists here or virologists that want to correct this—in terms of the stability of the phages and the amount of phage that were actually delivered. So I think that making sure that, you know, prospectively addressing any potential complications that CMC issues introduce.

And again, I think the main issues for future trials really involve, you know, identifying, you know, the correct dose, route

of administration, etc., as part of the clinical trial design and incorporating some of the elements I discussed earlier.

Does that answer the question?

DR. PENZINER: Yes, it does. I appreciate that. Thank you.

DR. REINDEL: So, I have Jerry Pier says, "Will the FDA require proof of principle for actual specificity of the activity in either preclinical or clinical studies by documenting outcomes such as lack of efficacy against a resistant organism? Most published preclinical studies use PBS controls, raising the potential that activity is due to something like nonspecific activation of the immune system."

So, I guess that question is, if I'm understanding it correctly, how do we know that this is—you know, how would we characterize potential off target efficacy? Am I understanding that correctly?

DR. PIER: Well, yeah, that's one question, but the other question is the design of most preclinical trials doesn't take into

account that there are other possible explanations for the outcomes being reported such as an immunomodulatory effect. So, is that going to be something the FDA would want to see in preclinical data or in clinical trials to see if you are or are not getting efficacy against resistant organisms? The data showing specificity of these phages *in vivo* is really highly confounded by a lack of these types of investigations or controls.

DR. REINDEL: I think that is a great question about whether or not you would want to look. I think the complication—I'm just trying to think about this a little bit on the fly in terms of how you would design a clinical trial in terms of using a phage when you know you have a resistant organism, and how you would address any potential, you know, safety concerns or concerns about giving a treatment that theoretically you know shouldn't work. So, that's a good question and I need to think about it a little bit more, about how you would incorporate that specific question into a clinical trial design.

DR. PIER: Okay, thanks. I think preclinical models could clearly be used. Clinical trials would be a little bit more difficult, but it would be possible to get information. But clearly, when the IND meeting comes up preclinical data are looked at.

DR. REINDEL: Yeah, and I think in terms of, you know, I think the helpful preclinical studies that can be used to address that. I'd have to defer to my CMC colleagues, not to turf it, but, you know, in terms of how you design those studies and which are going to be most informative in terms of translating to human clinical data.

Okay. From Jane, for those of us accustomed to thinking about antibiotic trial designs, the FDA guidances on the core indications are sacrosanct. Are there notable areas where phage trials should/could diverge from these FDA guidance documents? Can you give me --

DR. KNISELY: Sure. So if you have a gram-negative antibiotic, typically you go for a complicated urinary tract infection, maybe a

complicated intraabdominal infection, indication first, then you might add nosocomial pneumonia. If you have a gram-positive, generally it's skin and soft tissue infection. Like, these are pretty well-trod pathways that antibiotic developers tend not to diverge from. And I'm just wondering as phage developers enter the clinic how closely they should be, you know, paying attention to those guidance documents. I don't have insight into how the FDA develops guidance documents like these, but I would presume that they are developed primarily by CDER. And so, I don't know if they're developed with the lens of, you know, a more nuanced development program maybe, like a phage development program might be.

DR. REINDEL: So, I know there are guidance documents that are center-specific, and there are some that incorporate from both centers, and that's usually written on the guidance, so you can see, sort of, who's signed on to that guidance. But I think, you know, are there situations in which the

clinical development programs might diverge? I suppose it's certainly possible. You know, where specific considerations based on the clinical development program, the product, etc., you know, how you're developing it. You know, will it be developed under the LPAD pathway, etc., which targets very specific limited populations? That may be areas where there's—we're able to have discussions.

And again, that's just to put a plug in to have—really engage with us early on in your development program so we can consider those kinds of requests in the context, the specific context of your product, your development program, the available preclinical and clinical data, etc., so.

DR. KNISELY: Thanks. And I just pulled up the cUTI one, and thank you for noting that it does say which centers developed it. And I think that one is a CDER guidance document. So, not to say that it couldn't be useful if you were thinking about that indication, but engage early with FDA and don't feel like you need to be—to stick to

those—what's laid out in those guidance documents necessarily.

DR. REINDEL: Yeah, I mean, I think we—you know, if you don't want to stick with that, you know, kind of ask us, discuss that with us. I would put it that way. I think, you know, if there's something in the guidance document that you think, for whatever reason, may not apply, or you want to discuss it further, certainly, those are questions that can be brought to these pre-IND, end of phase two-type meetings or, you know, if you have fast track or breakthrough, you know, more frequent meetings, etc. So, I think the answer is I couldn't answer or promise anything because it's all so contextual. But certainly, you can always ask the question.

DR. KNISELY: Thank you.

DR. REINDEL: Sure. So Lilian Li says, "Could you comment in a general way, regardless of phage or not, in a disease or patient population where ineffective standard of care exists, how can a sponsor design a clinical program with a goal to establish a

new monotherapy to replace standard of care from the FDA?”

Right, so that's sort of what I was getting at in terms of, if you want to use phage as standalone therapy, is that correct?

DR. LI: Ah, yes. I mean typically—can you hear?

DR. REINDEL: I can. Yes.

DR. LI: Thank you. Typically, when there is standard of care you would (inaudible) how do we take it off?

DR. REINDEL: Yeah, again, and that's part of, I think, the challenges that are specific to phage therapy. And I think really, there are so many elements that inform that discussion that I think have been addressed in a lot of other sessions today in terms of, is there a synergistic effect of phage with antibiotic? You know, and if so, is there an advantage to standalone therapy? Is there, you know, is there—are there data to support use of phage alone? Do you have some proof of concept or effectiveness data that would support phage alone?

I think if there's—in general, if there is no standard of care available, the discussions about the clinical trial design in terms of comparator groups will be a little bit different than if there is standard of care. And I think in general for infections, there's always, you know, with multidrug-resistant organisms, you may not have any antibiotics to which the organism retains any susceptibility. In which case, the discussion might be different. You know, that is, thankfully, rarer than the alternative where you do always have some antibiotics or some antibiotics that you could use even in the face of, you know, *in vitro* resistance that may still provide some clinical benefit, so…

So, from G. Mitropoulu, apologies if I mispronounced, "One of the reasons why some randomized controlled trials failed was because the causative agent was resistant to the phage. So, if a personalized approach is preferred, to administer a phage that is effective against a pathogen, you'll probably

need to administer different phages. Right?”

Yeah, so that's a great question. And I think one that we've thought about quite a bit because one thing I didn't get into in my presentation is sort of this idea that, you know, you can have a fixed—as you move into development you can have a fixed cocktail of phage, that, you know, that you sort of more maybe empirically or if you have some sort of companion diagnostic or something where you say, if your organism is susceptible to one or more of the phages in this cocktail, you can go ahead and use it.

And then there's the personalized phage, where it really embodies the essence of this push towards personalized medicine where you would get the phage that is the most—or phages that are the most active, and perhaps if you're using multiple, synergistic together against your specific organism, which would really be ideal and, as the field progresses and develops, maybe even more exciting things like, you know, phage that have phenotypic character—I’m sorry, have characteristics that

are associated with reversion of the bacterial phenotype to a more susceptible one.

That would be really exciting and great. But how do you do that when people are getting different—you know, everyone's getting sort of their own different product. And there are a lot of considerations that go into the regulation of that, in terms of, you know, CMC information that would be provided from that kind of system would need to be provided.

Also, you know, what are you licensing? Are you licensing sort of the process by which you identify and manufacture the phage? Are you licensing the outcomes? And how are you addressing in the clinical trial design all of the variability therein, in terms of, you know, concomitant antibiotics, the fact that each phage-host interaction is so highly specific and may vary?

So, that's an excellent question, and I think one that I'd love to hear the input from others on any thoughts or ideas about that, but definitely something that we're thinking about and considering.

Again, I'm only just, staring at a picture of myself, so that's the hazard of me Zooming things. I don't know if everyone's packing up their stuff to go because the time is over or people have additional thoughts or questions, but I wanted to say thank you to everyone, and I really appreciate everyone's really thoughtful and helpful questions, and just open up the floor for anyone else to speak or address anything anyone else has said. It doesn't really have to be me or John.

DR. FIORE: Hi, this is Cara. I'd like to make a plug for everybody on the line to when they ask—when they submit something like a pre-IND meeting request, to really ask specific questions in terms of study design. They are—and give us their plans long term. I know Dr. Reindel spoke about it, I've mentioned it, and others, but it is super important for us to get an idea of how you plan to use your product at the end of day. And it will definitely inform our review and our feedback that we give you. So, I think this has been an excellent discussion, and we

like to see this type of discussion, but also that, you know, don't be shy about asking specific questions during pre-IND meetings and in your briefing package, so that we can give you as thoughtful feedback as possible.

DR. REINDEL: Okay. Well, I don't know if it's my job to wrap up the session or if someone else is supposed to do it.

DR. KNISELY: Sure, go ahead.

DR. REINDEL: Okay. Sorry, I wasn't sure, Jane, of your protocol here. Again, thank you all for attending. And, you know, we at the FDA really enjoy what we do and interacting with you. And as Dr. Fiore mentioned, we look forward to scheduling meetings with you to discuss all of these in the context of your specific clinical program. Thank you.

DR. KNISELY: Thank you so much.

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

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