FOOD AND DRUG ADMINISTRATION (FDA)

CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

PUBLIC WORKSHOP:

FACILITATING ANTIBACTERIAL DRUG DEVELOPMENT FOR PATIENTS WITH UNMET NEED AND DEVELOPING ANTIBACTERIAL DRUGS THAT TARGET A SINGLE SPECIES

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P R O C E E D I N G S

8:30 a.m.

WELCOME AND INTRODUCTIONS

DR. COX: Good morning. Good, the microphone's on. Welcome, everybody. I'm Ed Cox. I'm director of the Office of Antimicrobial Products. And can folks here me? We're good? Okay. I just want to start out by welcoming everyone. I'm still getting myself oriented here at the podium a little bit -- to our public workshop on facilitating antibacterial drug development for patients with unmet need. And just so that folks, you know, understand, I mean, this is a workshop. It's not an advisory committee. So it really is an opportunity for discussion. It's not really an exercise in achieving consensus.

We do provide conflict of interest information, which I think is available at a table out front, if folks are interested in seeing that. And we'll also, later on in the day, have an open time for comments for anyone who wishes to provide their viewpoints. And I thought what we'd do first is just

go around the panel and have folks introduce themselves this morning so that folks know who is on the panel. And maybe we'll start on my left with Kert. And please just introduce yourself and use the microphones so that folks, both on the webcast and in the room, can hear you.

DR. VIELE: Hi. I'm Kert Viele, from Berry Consultants. I'm a statistician.

DR. RUBIN: Good morning. I'm Dan Rubin, a statistical reviewer at FDA.

DR. AMBROSE: Hi. I'm Paul Ambrose, from the Institute of Clinical Pharmacodynamics, a PK/PD guy.

DR. FRIEDLAND: Ian Friedland. I'm the chief medical officer at Achaogen.

DR. REX: John Rex. I'm an internist and ID specialist at AstraZeneca Pharmaceuticals.

DR. KARTSONIS: Nick Kartsonis. I'm an infectious disease clinician and I work at Merck.

DR. CAVALERI: Marco Cavaleri, head of anti-infectives and vaccines, European Medicines Agency.

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DR. LARSEN: Joe Larsen, acting deputy director at BARDA.

DR. LOUIS: Tom Louis, Johns Hopkins, biostatistics.

DR. DIXON: Dennis Dixon, NIH, NIAID.

MR. DANE: Aaron Dane, statistical consultant.

SESSION 1: GENERAL CONSIDERATIONS FOR UNMET NEED PROGRAMS

EFFECTIVENESS STANDARDS INCLUDING ORPHAN PRODUCTS

DR. COX: Great. Thanks, everybody. And we appreciate all that have come to join today and all the panelists that have also traveled far and wide to come and join us. And let me just -- I'll just

briefly walk through -- I think folks have the agenda, so I'll briefly walk through some nuts and bolts. This morning, we'll talk about general considerations for unmet medical need development programs. We'll have a series of talks, you know, describing different pathways. And then, as we move on in the day, we'll actually hear from a couple of folks that have, you know, tried to venture into this area. They'll share with us their experiences to date, what's worked, what they've run into as far as the challenges in doing such programs. So we appreciate their willingness to provide us with those details. I think that'll be very helpful.

And then, later in the afternoon, we'll have some discussion about statistical considerations for developing antibacterial drugs using an unmet need paradigm. So I just want to provide a little bit of background and some context. You know, we typically find that as we're preparing for a workshop, oftentimes there's a lot of very rich discussions during the course of the preparations for a workshop.

So what I'm going to try and do -- my talk

is a little bit disjointed. But I'm going to try and touch on a number of the issues that came up as we prepared for today's meeting because I think that may be helpful. You know, folks know that the antibacterial drug development area is particularly challenging. Scientific reasons make it difficult. You're not exactly sure what the patient's diagnosis is. The patient may need other overlapping therapy that can obscure the assessment of the drug that's being tested. There's a lot of drugs out there, but there are still patients who -- for whom those drugs are not good options because of the development of resistance.

Economically, it's also challenging, not within the scope of what we'll be talking about today, but there has been a lot of important work looking at the economic issues for antibacterial drug development. And also though it's not really parsed into these two poles, but more of a continuum, we do see antibacterial drug development in terms of standard development programs. These are the more traditional development programs where there are

molecules that are being developed using sort of traditional NI margins, traditional study approaches. And then, on the other end of the pole is the area of unmet need development programs. So these are development programs that are characterized typically by a greater degree of uncertainty and it's not a decision per se to go one way or the other based on the absence of information about the drug. Actually, the drug and its characteristics are very important in determining which pathway one might choose.

For a molecule that is pursuing an unmet need development program, there really has to be a particular characteristic that make it a reasonable choice, such as it's a molecule that operates via a new mechanism of action. It's otherwise stable to resistance mechanisms that would otherwise chew up a molecule or it's paired with a resistance inhibitor or something of that nature. So we know the current antibacterial pipeline is quite fragile.

There have been some changes that have happened over the last several years that have helped some, with passage of GAIN, the qualifying infectious

disease product legislation that came in place, which provides for fast-track designation, priority review and an additional five years of exclusivity for drugs that qualify. And the QIDP designations so far are up to 63 different unique molecules, probably the more important number. The 107 is sort of a factor of how you split up -- if you look for different formulations or different indications. So 63 is probably the number to index off of here. And then, we have to keep in mind that, in general, most drugs that enter into Phase I are not ultimately shown to be safe and effective. So although these numbers sound quite large, you know, some of them may -- some of them won't make it we know just based on experience.

And it's also important to keep in mind too that when we think about bacterial diseases and antibacterial drugs, that the response that a patient experiences is not just the antibacterial drug, but there's also the immune system, tissue repair and other events going on that happen as the patient moves from being ill to being better. I won't spend much time on this slide. But folks are aware of some of

the recent approvals for antibacterial drugs and I've included in here also a drug for TB. And unmet need, so if we think about unmet need, how do you get there. Well, if you have a less than robust antibacterial drug development pipeline, it provides an opportunity for resistance to essentially get a little bit ahead. And so, a situation where you have unmet need is actually something that you prefer to avoid. You don't want to end up in a situation where you have bacteria that are resistant to multiple drugs such that you have patients who lack good therapeutic options.

So ideally, if you have ongoing development that's robust, you can have agents already available that have already been shown to be safe and effective prior to the point in time that you need them. And we know already that it's difficult to react in a timely fashion once an unmet need has arrived -- has arisen. You know, it may take 5 to 10 years to develop a new antibacterial drug. So a resistance mechanism that pops up today, to embark upon a program at that point in time is really not a timely way to respond.

Sumathi will go into a little more detail on trial design options for unmet need. But here's some of the different options that you might think about, a non-inferiority trial design. You can do it in a body site of infection. Superiority trial in one body site or you could do something pooled across multiple body sites. And Kert will talk some about some of the work that his group has been doing on this a little bit later today. Nested NI superiority trial designs based upon the patient's baseline isolate. And we've also seen development in the area of .-lactams that have been previously approved paired with new .-lactamase inhibiters. In this situation, you can rely upon the previous finding of safety and efficacy for the previously approved .-lactam drug. Another area too where there's some activity is that of showing superiority of an adjunctive therapy with standard of care over standard of care.

And let me talk some about non-inferiority trial designs. You know, this is an issue that comes up. It's a topic of which there's really much discussion. And Sumathi and I and some others wrote

on this even a couple of years back. I think it was in 2014, in the summertime. If you think about it and what the circumstances that you need to have in order to be able to show superiority, it's likely time-limited. It really is dependent upon enrolling patients with, you know, resistant phenotypes for which you have inadequate options. And this could be really challenging, particularly if, you know, patients who have, you know, few options are -- you know, if the frequency is not that high.

And if you think about it, if this is a very difficult paradigm to follow, you could take a good drug, an effective drug and run into challenges and difficulties in conducting the clinical trial. So you're not really just testing the drug. You may also be testing the test. And if the test is one that really is not achievable, the drug may fail because the test can't be performed, not because the drug wouldn't have otherwise been shown to be effective. And we really don't want to wait for the incidence of highly-resistant organisms to be high enough to make superiority trials easy enough to perform.

I mean, some would argue if that's the circumstance that you've gotten yourself into, you've not done well. And we have to keep in mind too that when you're studying best available therapy and trying to show superiority over best available therapy, best available therapy may actually have some effect. Resistance is not a binary, you know, hundred percent or zero percent. It's a continuum. So you may have a lesser likelihood of response. But it's not going to be zero. So best available therapy may have some effect which may make showing superiority somewhat challenging. What I mean by that is it's not that the new drug isn't better. But the effect size may be not so -- not as large as you might expect initially without sort of putting more thought into this.

So the trial may be one of considerable size. And if you think about a trial that's designed to show superiority and the reason that you can show superiority is that the options currently available are not that good, once a new standard of care has been demonstrated, the ongoing trials would, from an ethical standpoint, need to include that standard of

care. So there may be a certain degree of unpredictableness/uncertainty that may accompany doing a superiority trial.

So just thinking about, you know, if you take a non-inferiority approach, the drug that you study, you may not actually elicit all of the attributes of the drug in a non-inferiority trial. There may be mechanistic reasons that the drug will have utility and preserve its activity; again, certain resistant isolates that may not be enrolled in the non-inferiority trial because patients in that trial would generally be ones in whom you would want the comparator drug to be effective. We can talk more about the nested superiority/non-inferiority.

And then, just one last final point and that is as we think about where the drugs that we use today came from, including the drugs that we use to treat patients who have resistant organisms, they were -- many were studied at a time when the resistant phenotypes of concern didn't even exist. So, and superiority trials, you know, I'm trying to get to sort of the practical issues here. There's no

question superiority trials provide clear evidence of efficacy and that they are easy to interpret and that they don't have some of the trappings of a non-inferiority trial.

But they can be challenging to conduct, as I've just discussed. And through the course of the presentations today, I think you'll hear some more details on this. We understand that some folks are interested in such claims. You know, and we're more than happy to work with folks that are wanting to do, you know, superiorly trials. But we think it's important that folks think about this and, you know, balance some of the issues with achievability, you know, so that the drug can be studied if you run into particular challenges if you're trying to pursue something in the area of superiority. And some have raised too issues with regard to generalizability using a non-inferiority approach. And that's something we can talk about a little bit more today too.

And so, here I'm jumping around a little bit. But you know, just thinking about some of the

challenges that we face in antibacterial drug development, if you contrast serious acute bacterial diseases with oncologic conditions, HIV, hepatitis C, rare metabolic disorders, and go through sort of a couple of different characteristics -- and I'll just do this informally. I don't know that it's engraved in stone or that I've got it completely correct. But I'd welcome your thoughts on this too.

But if you think about it, identifying patients -- well, for serious acute bacterial diseases, it can be really any of a number of different folks across the globe who may show up with, you know, an acute infectious disease caused by bacteria. And they'll show up, you know, quickly, whether they're already in the ICU or they present to the emergency room. You know, and for an oncologic condition, usually you're going to have a tissue diagnosis. You're going to know who these patients are; likewise, for HIV and hepatitis C. For rare metabolic disorders, the patients may be in a registry of care at a referral institution. So it's a much more defined population.

So that's one issue that can make studying a drug for an acute bacterial disease quite challenging. The disease course over time for most serious acute bacterial disease, it starts, you know, quickly and it ends fairly quickly. So the period of time to either enroll a patient in a trial or, you know, study an intervention is very limited. It makes it, again, very challenging. And that's not quite the case -- I mean, the other disease -- you know, you may want to intervene within a relatively short period of time. But the time pressure is much different, in my opinion.

Diagnostic certainty -- for the patient with a serious acute bacterial disease, is it pneumonia, is it heart failure, is there something else going on here. You know, just think about the patient in the ICU with HAP/VAP and the challenges of making that diagnosis. And you know, again, for these other conditions, typically you have a fair degree of diagnostic certainty. We've already talked about the urgency of the situation. For acute infectious diseases too, there may be considerable variability in

outcomes. You know, when I talk with my colleagues in the oncology group, they oftentimes will tell me, you know, that the tumor won't shrink. It simply doesn't happen.

So if you have a lights-on/lights-off phenomenon, you know, an ammonia level that's going to stay up here absent an effective therapy -- things could be quite different in an acute bacterial disease and it could make things fairly challenging. Also the opportunities for rescue for serious acute bacterial disease, the opportunities for rescue may be really quite limited. You know, you may jump in there. But given the serious nature of the disease, the rapidity with which it can progress -- and for some of the other conditions, there are opportunities to jump in there and come in with another therapy.

So you know, a credit to all the folks that are, you know, here today working on what is an important but also a very challenging area of antibacterial drug development. Clinical trials continue to teach us new things, many of which we didn't necessarily expect and that we would have hoped

to have avoided. So I think it's important -- and I won't go through these, but I thought it would be helpful just to have them out there, all based on information that's out there in the public. You know, we see that some drugs didn't pan out in certain conditions. Some drugs didn't appear to work as well as their comparator.

And some of these things are surprising to us. We see some that work in some indications and then some that have troubles in others. So you know, it may be intrinsic characteristics of the drug. It may be the dosing of the drug. There may be other things going on here that weren't necessarily expected. And again, I'm jumping around a little bit. But one of the things we hear sometimes is that there isn't much going on in HAP/VAP and HAP/VAP is really challenging to study. There's no question about that. I don't think there's any debate.

But if you go to clinicaltrials.gov, you can actually see there are a handful of studies going on in HAP/VAP and that's good news. So and typically what we're seeing is that folks are doing, you know,

complicated intra-abdominal, complicated UTI indications and then subsequently moving on to the more challenging indication of HAP/VAP. So if we think about antibacterial drug development too, it's important that we continue to advance the science. This is a challenging area. You can tell we're dealing with a fair degree of uncertainty in some situations in order to, you know, have drugs that can be studied, that can be available for patients.

But it's also important too that we continue to tend to the science. And the folks at the FNIH have been working on developing and evaluating endpoints. The folks at CTTI are doing important work looking at trial efficiency and design. They have a very important project, in my opinion, in HAP/VAP, trying to figure out how they can make HAP/VAP trials more efficient and they're progressing well on that. And the Duke-Margolis Center has been looking at overarching issues in antibacterial drug development and, you know, has a conference following this on economic development. We work at our colleagues at EMA -- and we're very glad that Marco came over to

join us -- you know, through our confidentiality agreements. And we've found those interactions to be very helpful. It gives us a chance to share opinions on development programs and on approaches to development. And I think really an important theme here is that curating the science supporting clinical trial design and endpoints is key both here in the United States and for harmonizing available approaches internationally. And there's no reason, if the science is there, that we shouldn't be able to do similar things.

You know, whenever somebody holds a workshop, it's an opportunity to talk about all the issues that we face. And I think it's important to recognize right from the start that it's important that, you know, we recognize the multifaceted nature of the challenges that we face. And FDA plays an important part here. But I think there's also a lot of other groups that are involved. And you know, I've listed a variety of the different areas and I think folks will recognize, you know, resistance surveillance for the prevention of infection, a lot of

work of colleagues in stewardship, a lot of colleagues at the CDC research and development. We're glad that Dennis could join us here from NIAID.

And there's an important role of academia, industry and government, hospitals, patients, society in general because of the issues around antibacterial drug use. Professional societies publish treatment guidelines and provide, you know, other advice to practicing physicians. Public-private partnerships and payers all play a role here. And I think it's important that we keep that in mind as we work through the day. So to overcome these challenges, we'll need a variety of different solutions to deal with the multiple different factors that we're facing and the challenges of antibacterial drug development, the use of these drugs, antimicrobial resistance.

It's important that basic science, R&D continue to feed and develop new lead molecules for early development that then progresses through advanced development. Again, colleagues from NIAID, Joe Larsen from BARDA is also here with us today. And I think too, you know, the value of new antibacterial

drugs, you know, if we look at some of the economic reports -- and I've cited the RG report here -- you know, the societal value of having a new antibacterial drug exceeds its private value. So there's a little bit of an imbalance here that suggests the need for, you know, continued work on incentives to try and be able to get things in balance with regard to the value of these drugs to society.

Another very important area I think that could help advance the science in this area is that of a clinical trial network. And our colleagues from BARDA recently put out a request for information to understand a little bit more about what might be involved in developing a clinical trial network. And when we talk about a clinical trial network, at least in my mind we're talking about infrastructure so you avoid having to start up each time. So you know, you do a HAP/VAP trial, you're not just starting from square one and the last group that did one just sort of deflated all their infrastructure.

This should allow for the development of expertise, the lab support being in place and ideally

there'd be a common protocol that would be used for each of the several drugs. It could also allow for the concurrent study of a couple of drugs at the same time. And it also may serve important roles too for developing diagnostic tests, another important area. I mean, if diagnostic tests can be developed, that could transform the way that antibacterial drugs are utilized out there and used more prudently and could also help some with clinical trials too.

And just if folks are unfamiliar with sort of a common protocol or master protocol idea, here's a schematic of what one might look like. You have a control group on top and the control group is shared between the drugs that are enrolled during the same time period and you can see drug A in blue is the first experimental drug. So during that initial period, it's drug A and the control, to which patients are randomized. Drug B is introduced in that second segment and there control patients are shared between drug A and drug B. And then, subsequently drug C pops in and all three share the control group. So you have three drugs being studied concurrently. Drug C is

monitored and stopped early for futility and drug B continues on to be studied throughout the duration there. Drug A finishes a little bit early and is analyzed.

So there are certain efficiencies here, certain development of degrees of expertise that could be gained with a master protocol. There's no question there's fixed costs. There's a lot involved in setting up such an infrastructure. But it seems like there's an area where such approaches might help. So I want to stop there. I know it was a little bit disjointed. But I wanted to cover sort of a variety of different topics that have come up, done so in sort of a whirlwind fashion.

And now, I want to introduce Sumathi Nambiar. Sumathi is the director of the Division of Anti-Infective Products and also a very good colleague. And she will be providing us a talk on -- let me make sure I get my classes on here -- trial considerations for unmet medical need. So she'll be walking us through some of the nuts and bolts of unmet medical need development. So Sumathi, it's all yours.

TRIAL CONSIDERATIONS FOR UNMET NEED

DR. NAMBIAR: Thank you, Ed. Good morning, everybody, and welcome you to this two-day workshop. Can you hear me okay? All right. Okay. I'm going to try and build upon some of the principles that Ed has laid out in his talk. So here are some criteria that typically drugs have to be met -- can you hear me? Sorry. This is better? This is right in my face. All right. Okay. It sounds like you can hear me. All right.

So these are some of examples of types of antibacterial drugs that might be suitable for an unmet need development pathway. This is not an all-exhaustive list. But if you have a product that acts via a new mechanism of action or has an added inhibitor that can neutralize a mechanism of resistance or the activities preserved in setting of resistance to other antibacterial drugs would appear to meet an unmet need. I just want to emphasize this point because more recently we are seeing proposals for bridge [ph] programs without a real good justification for why one thinks the product actually

meets an unmet need. So one needs to spend a little bit of time and effort to really justify and make it clear as to why a proposed product has the potential to meet an unmet need.

So in general, for unmet need programs, smaller data packages are acceptable and hence such programs, there will be greater uncertainty about risks and benefits. Single, adequate and well-controlled trial may be adequate. We need good support of evidence to support that single trial. And it's very important that this thorough evaluation of the activity of the drug in vitro and in animal models of infection to support the smaller clinical data package. Healthcare communities should be aware of the uncertainty, both around risks and benefits, and these risks and benefits and the shortcomings will be communicated appropriately and labeling. And labeling from such programs will include a limited use statement.

We expect adequate in vitro data and activity in relevant animal models of infection, adequate evaluation of PK/PD relationships from animal

models of infection. It's very important, and I cannot emphasize this enough, that understanding the PK in patients with renal or hepatic impairment early in development is very important because this will facilitate enrollment of such patients, as they often have important comorbidities. And you'll see this theme come up in subsequent presentations. I think it comes up in Dr. Friedland and Dr. Dudley's talk, where how patients with unmet medical need are in fact a little different from patients who typically enroll in some of these trials. So I think this is very important. And also it's important to collect PK data in clinical trials.

I just want to remind everybody that drugs being developed to address unmet medical need must meet the statutory standard for effectiveness where substantial evidence is defined as evidence consisting of adequate and well-controlled investigations. And an adequate and well-controlled study is described in 21 CFR 314.126. Since the passage of FDAMA, you know, we are allowed to -- I think they sort of clarified that we could consider data from one adequate and

well-controlled clinical investigation confirmatory evidence to constitute substantial evidence. And every often in discussions that come up that the standards might be different for products which are designated as orphan and orphan drug products do still need to meet these statutory requirements.

So we go through some trial design options. I think as Ed has already mentioned, we are of the opinion that well-conducted non-inferiority trials are important to maintain a robust pipeline of antibacterial drugs to meet patient needs. Treatment options should be available before new mechanisms of resistance emerge, and if we are in a situation where these trials are in fact easy to do because levels of resistance are so high, then antibacterial drug development has not kept pace with emergence of resistance.

A well-conducted non-inferiority trial will provide evidence of a drug’s efficacy in a given body site of infection and in general these trials will be limited to situations where the baseline organisms are susceptible to both the test and comparator drug. So

these trials often enroll few or no patients infected with multidrug-resistant phenotype organisms. But the evidence for this activity against those particular phenotypes comes from the drug's activity in vitro and in animal models of infection.

So what might be some options if one wants to conduct a non-inferiority trial? A single trial at any one body site would be acceptable. As I mentioned earlier, it's important to enroll patients with severity of illness or comorbidities which might be similar to those seen in patients with unmet need. We are willing to accept a wider non-inferiority margin than one would accept for a traditional development program. Data from such a trial could be supplemented with data from a study in patients with infection due to the specific phenotype of interest. From such a study, one can obtain PK data and in a sicker population or patient population that has comorbidities. And it also provides some clinical experience in patients with infections due to these specific organisms, which we've heard from our clinical colleagues is very valuable to them.

We've certainly had a lot of discussion amongst ourselves whether it's possible to do a non-inferiority trial pooled across body sites. We do think that poses additional challenges, but we'd certainly be interested from thoughts from attendees at the workshop. I think some of our main concerns have been that the magnitude of treatment effect can vary across the infection types that one is attempting to pool. The endpoints are highly variable. And I think, very importantly, such a trial may not demonstrate if there's a potential deficit in treatment effect across the different infection types that are pooled. And we've seen examples of drugs that have worked in one or more body sites and not worked in other body sites. And Ed had shown us a slide which sort of gave examples of recent experiences.

One can certainly do superiority trials. It provides a clear finding of efficacy. But we do think it poses -- it is extremely challenging to do one of these trials. And again, this will come up in discussions and presentations during the course of the

day. We think the ability to rely on superiority is likely time-limited because once a new therapy becomes available, an ongoing trial which is designed to demonstrate superiority of a standard of care would likely become unethical because now you have other options available. And subsequent trials would need to be non-inferiority trials. Superiority trials could be at a single body site or one can pool across certain body sites, as long as you have a representative sample from each type of infection.

In a superiority trial, you can attempt to demonstrate superiority over active comparator. And I've said earlier, it's usually dependent on the comparator of the trial representing suboptimal treatment. In other words, it's very hard with the currently available therapies to demonstrate superiority. It does happen, but not very frequently, where an antibacterial drug is actually able to provide additional benefit over active standard of care. One recent example was a trial in complicated UTI with ceftolozane/tazobactam where superiority of ceftolozane/tazobactam over levofloxacin was

demonstrated. It's important to note that just over quarter of the baseline isolates in the comparator arm were levofloxacin non-susceptible. So this raises questions about whether one can in fact repeat such a trial, going back to the same study sites where the prevalence of levofloxacin non-susceptible isolates is that high.

There has been a lot of discussion and some interest in potentially using external controls in demonstrating superiority of external controls. And the challenges in using external control data are well-described in ICH E10. There's always a question of comparability between the treatment and control groups because they can differ not only in what we know -- so the known risk factors, but also in unrecognized or inadequately measured risk factors. And it's very well-documented that untreated historic controls tend to have worse outcomes than an apparently similarly chosen control group in a randomized trial, possibly reflecting a selection bias. As a third option for superiority trial would be a product that is being administered in addition to

standard of care, some kind of an adjunctive therapy within the test drug plus standard of care is compared to standard of care versus placebo.

So again, I mentioned this earlier in superiority trials. We're willing to consider pooling across body sites. So for a Gram-negative drug, pooling, you know -- pooling across cIAI, cUTI and HABP/VABP is acceptable. We do recommend that at least half the patients have HABP/VABP because this is one indication where we've seen deficits in performance of antibacterial drugs. There's been more than one example. In such a trial, patients with document infections due to a certain resistant phenotype would be enrolled; for example, carbapenemase production. Best available therapy would be used as a comparator. All-cause mortality or disease-specific definition of clinical success is acceptable. And we've considered allowing the use of one-sided alpha of 0.05, given that the comparator regimen will have some treatment effect. And again, you'll see this in an example later in the day.

One other option, which I know we've all

discussed a fair bit, but we've really not seen a proposal come forth is a nested non-inferiority/superiority trial design where in a subgroup of patients that have the -- of a resistant phenotype, one can attempt to demonstrate superiority. So you remonstrate non-inferiority in the population susceptible to comparator and superiority in the subset of patients that have baseline organisms resistant to comparator. Here if a superiority is not demonstrated, it does not in fact impact the conclusion of non-inferiority.

So I thought what I would do next is just walk you through maybe three or four potential scenarios of what development programs can look like. Again, I think it's very important to note that it's really not a one-size-fits-all and these are general approaches. But we do have to make adjustments depending on the specific drug and the specific program. so in this example, if a drug has a -- it's a Gram-negative drug and it has a spectrum of activity that includes Enterobacteriaceae and P. aeruginosa. We have activity that demonstrates that this drug

works against ESBL-producing organism including serine carbapenemases.

So your potential options could be a single non-inferiority trial at any one body site. You could choose cUTI. You could choose cIAI. The benefit there is you could test the drug as monotherapy. Should you be interested in developing the drug for HABP/VABP, I think one really needs to address how the concomitant therapy that's used to treat P. aeruginosa and its impact on assessing treatment benefit will be addressed. And again, I think this is a topic that's going to come up hopefully today, but certainly in tomorrow's discussion. Again, superiority trials are an option. This could be done at a body site, any of the body sites that I have listed above or a superiority trial where one pools across body sites. And a third option would be a nested non-inferiority/superiority trial.

A second example is if you have an antibacterial drug that only is active against a single species; for example, P. Aeruginosa, A. baumannii. We understand there is interest in

developing such drugs and we will spend a whole day tomorrow talking about this. So I'm not going to go into further details.

A third example, and we do see a fair bit of this particular option, is a new ß-lactamase inhibitor which has been combined with an approved ß-lactam antibacterial drug. And under section 505(b)(2) of the Food, Drug and Cosmetic Act, we can rely in part on our previous finding of safety and effectiveness for the corresponding approved indications for the ß-lactam drug. And this can provide part of the evidence needed for the BL-BLI combination.

Again, as I said early on, it's very important that if you are using this sort of an approach, that you provide adequate justification that the addition of the ß-lactamase inhibitor addresses an unmet need. We need robust evidence of the contribution of the ß-lactamase inhibitor in restoring the activity of the ß-lactam and this can come from in vitro studies and from animal models of infection. We need adequate dose rationale, including the appropriate ratio of the ß-lactam and the ß-lactamase

inhibitor. And importantly, we need -- even though we can rely to a great extent on what we know about the ß-lactam from previous approval, we need adequate safety data for the ß-lactamase inhibitor and the combination product.

The clinical data package for such a drug could vary. It really depends on the approved indication for the ß-lactam. So it depends on which ß-lactam you are choosing, what that is approved for and the indications in which the BL-BLI have been studied. So you could consider doing a single, adequate and well-controlled non-inferiority trial in a body site of infection and such a trial does not need to be enriched for organisms that are non-susceptible to the chosen ß-lactam. We've also considered smaller trials in indications for which the ß-lactam is approved, as in the example of ceftazidime-avibactam that was approved last year. And such a trial ideally should include some patients with infections due to the ß-lactamase-producing organisms.

Lastly, if one is looking to develop a

product that will be administered as adjunctive therapy to standard of care, some examples would include inhaled antibacterial drugs being developed for ventilator-associated bacterial pneumonia, immune modulators, monoclonal antibodies targeting a specific organism. The trial design would need to be a superiority trial where the test drug plus the standard of care is compared to the standard of care.

So in summary, we've laid out some potential development pathways for a drug that has a potential to address an unmet need. One could do a non-inferiority trial at a single body site. We're willing to accept a wider non-inferiority margin. And one could include a nested superiority option, if desired. If one wants to pursue a superiority trial, such a trial could be done at one body site or you could pool across relevant body sites. And the drug -- the test drug is compared to the best available therapy.

If the drug is being used as an adjunctive therapy, then you add it to the standard of care and compare it to standard of care plus placebo. And if

it's a new ß-lactamase inhibitor being developed that's being combined with an approved ß-lactam antibacterial drug, one could rely in part on Agency's previous finding of safety and effectiveness of the approved ß-lactam. Thank you.

[Applause.]

DR. MARKS: Thank you, Ed and Sumathi. What a great start in terms of the clarity with which the regulatory environment in the U.S. has evolved, where I think many of us see the Agency as being part of a solution clearly as we try to deal with this difficult issue. And now, similarly on the other side of the ocean, we have Marco Cavaleri, head of anti-infectives and vaccines at the European Medicines Agency talking about the regulatory pathways and approaches to unmet need. And I would give a similar comment about Europe as well in terms of being part of the solution. Thank you.

REGULATORY PATHWAYS AND APPROACHES TO UNMET NEED

DR. CAVALERI: Thank you very much, and good morning. I would like to really thank Ed and Sumathi

for the invite. It's a great pleasure for me to be here and to present the perspective of the EMA. And as Ed said, I think it's important to stress also the fact that the EMA and FDA has been continuously discussing over the last years about options for developing of new antibacterial agents and particularly for those that might address unmet medical needs related to multidrug resistance. So again, it's a great pleasure for me to be here and presenting the European perspective and discuss with you options.

I was asked to start with to describe to you very briefly what is -- what are currently the approval pathways according to European legislation for medicinal products that could also apply to medicinal products that address unmet medical needs. So one option is a full marketing authorization and maybe it's important here to also add that recently in Europe Union there has been approved a pharmacovigilance legislation which would allow the EMA also to pause study also in the context of a full marketing authorization as post-authorization safety

study or post-authorization efficacy studies, particularly in order to address uncertainties that are considered key to the benefit-risk of the medicinal products.

And then, I will talk more about conditional marketing approval and approval under exceptional circumstances which are the regulatory tools that we have in those circumstances where we feel they might be needed or would be expected that an approval based on less than normal level of evidence could be done. Then, the last option is the Article 58 scientific opinion for use only outside of the EU, which will not apply in this setting and therefore I will not bring you any further details on this.

So as said, one option that we have in order to come to, as we called it earlier, approval is the conditional marketing authorization. This will be based on a less comprehensive data package and subject to specific obligation in the post-approval phase.

The scope -- so the products that will be in scope for this pathway will be products that address serious debilitating diseases or life-threatening

diseases or products that are to be used in emergency situations, like pandemic influenza, or for orphan medicine or products. And the criteria which all have to be met is that the risk-benefit balance is positive for the product and is likely that the applicant will be in a position to apply comprehensive clinical data after approval and also that the unmet medical need will be at least in part fulfilled and here of course the wording is a bit strong. But of course it will have at least a clear impact on addressing an unmet medical need and also importantly that the benefit to public health for the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required.

The other option that we have is called under exceptional circumstances. And as the European law says, in exceptional circumstances and following consultation with the applicant, the marketing authorization may be granted subject to certain conditions, in particular relating to the safety of the medicinal product. And also, it goes on saying

that the marketing authorization may be granted only when the applicant can show that he is unable to provide comprehensive data on the efficacy and safety of the medicinal product under normal conditions of use.

And the grounds are set out in Annex I in which situations this might be applicable. In any case, it will be linked to an annual reassessment of the conditions. So and here are the grounds as per Annex I of the directive. So it has to be an indication for which the product in question is intended -- is rare, so that the applicant cannot be reasonably expected to provide comprehensive evidence or in the present state of scientific knowledge, comprehensive information cannot be provided or it would be contrary to generally acceptable principles of medical ethics to collect such information.

So to summarize the differences between conditional MA and MA under exceptional circumstances, in this slide I will try to summarize. So the conditional MA, full conditional MA comprehensive data are expected after authorization with the idea to

later switch to a full marketing authorization, while for MA under exceptional circumstances, comprehensive data are deemed not possible to gather and therefore is supposed to remain such indefinitely. The conditional MA is valid for one year only with annual renewals that have to take place, while the MA under exceptional circumstances has the normal validity of any other marketing authorization and goes through an annual reassessment procedure. The conditional MA applies only to centralized procedures while the under exceptional circumstances MA is possible in all registration procedures.

Now, a few words on the PRIME scheme, which is something brand new the EMA brought forward. And this is a scheme that is aimed to foster the development of medicines with major public health interest, so building on the existing framework and with an eligibility program that is according to the existing accelerated assessment criteria. And the idea here is to reinforce scientific and regulatory advice to developer in order to foster and facilitate earlier interaction, optimize development for robust

data generation, indeed try to work together with the developer in order to have an efficient development plan, and also enable accelerated assessment at the level of the CHMP.

So from this principle, this boils down essentially to first of all having a written confirmation of PRIME eligibility from the EMA following a submission of a request and the potential for accelerated assessment, an early CHMP rapporteur appointment during development, kickoff meeting with multidisciplinary expertise from EU network and enhanced scientific advice at key development milestone/decision points, including also the option to discuss with technology assessment bodies. There will be an EMA-dedicated contact point and fee incentive for small and medium enterprises and academics will be provided for their scientific advice procedures.

So now I give you a bit of an overview of the entire regulatory framework in Europe. And now, we will move more directly into the area that is discussed today and tomorrow, which is around the

development specifically for MDR pathogens in area of unmet need. And the position of the EMA is summarized in the Addendum to the Guideline On the Development of Agents to Treat Bacterial Infection and I would say that the position of the EMA has not changed since the issue of that document in 2013, even if of course we are having a lot of interaction with developers and we may amend or fine-tune some of the options that were provided in there.

So I will start describing you very briefly what is in that document and what are the main points that we would consider for developing new antibacterial agents in area of unmet medical need. Well, first of all, these products have to be eligible for the acceptance of limited clinical development and that might not be straightforward in all cases. First of all, there has to be demonstration that the investigational product has the potential for treating infection for which there are few remaining therapeutic options. There also there is a need of a good understanding of the impact of all possible resistance mechanisms on activity and not just

focusing on a few of the main ones as that is not telling you the entirety of the story.

So it's important that the microbiology and the PK/PD is already there to address the fact that this agent has the ability to address an unmet medical need. And if the product is active only on single genus or species, there should be justification that indeed the organism is problematic. So the possible scenarios will be from the rather easy one of a new drug in a new class or let's say new mechanism of action. That should be fairly straightforward. Or it could also be new drug of an existing class with a novel spectrum. Of course, the data, the micro data and the PK/PD data will be important here, or could be a new or known drug of an existing class which is coupled with a new protective agent. And the example of a ß-lactam with a ß-lactamase inhibitor is an obvious one, but might not be the only one.

Now, there is a range of possible clinical programs that could be considered here, depending on the properties of the agent assessed or whether it's limited or broader spectrum and also, importantly,

what is the aim of the developers in terms of level of claims and SmPC. And an example would be whether a specific indication for a certain type of infection is looked at plus an unmet medical need indication or only a claim for using circumstances of unmet need. It's important to stress, as I said before, that further evidence of safety and efficacy post-approval will be expected.

In the future, we might be more and more in the situation in which requirement for post-approval commitment will take place. This may come from pivotal studies that are already planned for additional site-specific indications by the developers or that also could be a rather easy one or could be prospective uncontrolled studies that might be needed depending on what are the uncertainties in the benefit-risk evaluation or observational data from registries. And again, also here to stress that at the EMA there are a lot of efforts to try to understand how much can be gathered from observational data, how much can be gathered from real-life data and to what extent such data could have an impact on

regulatory decision, which I think we are just at the beginning of that journey. But it's important not to forget about these aspects.

So one of the pillars in the development specific for MDR pathogens will be to conduct an extensive microbiology and PK/PD program to fully document expectations for the products in order to support the dose regimen to be tested, support plans for regimen adjustment in patient subject, to support the anticipated efficacy against the target multidrug resistant pathogens and to identify any type of infection in which it should not be used or may need a different regimen -- as an example, could be penetration in the ELF or binding with the surfactant, but there could be many other examples -- and then, confirm the regimen using PK data from patients and conducting exposure-response analyses during the clinical trials. So this is an important area where it might be difficult to gather conclusive evidence, but still efforts are expected to be put in place.

So I think it's important for me to stress that in the addendum and in the EMA guidelines, we are

not demanding for a single specific approach to be followed. But we are highlighting the potential option for clinical development. So in a way, we are kind of framing what are the possibilities that will be acceptable for the EMA in terms of development in the area of unmet need. And indeed, the goal has been to enlarge the portfolio of acceptable clinical development options besides the standard approaches in light of the unmet medical needs.

So the addendum illustrates circumstances which would allow either an indication for unmet need or both an indication for unmet need and a standard type of indication and also stress the importance to put efforts to collect data with target pathogens. Clearly there is an expectation from the CHMP that efforts are put there, particularly for the target in an unmet need indication. But of course we have to be realistic and pragmatic and the prevalence will drive the ability to collect such data at the end of the day. So we should not forget that. And also, last but not least, it’s important of discussing with European regulators the specificities of the proposed

program. And as I said, we are putting effort of discussing this whenever there is an application that goes both to the EMA and the FDA also with colleagues at the FDA to see what could be the potential way forward.

So in the addendum, essentially we are giving some examples of what could be way forward in the context of unmet need related to MDR. And the scenario one that we are bringing forward is not far from what Sumathi was describing before. So a single randomized non-inferiority study in one indication, that for Gram-negative targets should be studying HAP/VAP or intra-abdominal with standard alpha and non-inferiority margin expected or alternatively a study in UTI provided the PK extrapolation to other body sites possible. And the data with the MDR pathogens may derive from a limited controlled or uncontrolled studies. And in this sense, if the results are supportive and the evidence sufficient to draw conclusions on the benefit-risk, it will be possible then to grant an indication for both the unmet need and the selected type of infection that was

studied.

A second scenario would be in case the target is really the unmet need indication only. So it would be a randomized study in mixed infection types with a target organism, excluding infections likely to need different regimen or where PK is lacking, like meningitis, osteomyelitis as an example. Superiority, we don't believe it will be feasible, at least if we look at endpoint that will be the standard endpoint that we would require for type of infection. And the non-inferiority is also not possible as it will be impossible to define a non-inferiority margin in such context and with this mixed type of infection study. So what we would recommend in this case is not powered for formal inferential testing. At the same time, we would recommend that some comparison to look into superiority on secondary clinical endpoints could be explored nevertheless. Control therapy might need to be flexible, so best available therapy and this can be discussed and also tomorrow we will have a chance to discuss a specific case. And the use of experimental rapid diagnostic testing to enrich

enrollment would be fully supported. In this case, the indication would be for the unmet need.

A third scenario would be just to conduct an uncontrolled study confined to target organisms using historical and external controls. The justification would be based on the rarity of the target pathogens. The use of rapid diagnostic testing to enrich enrollment here would seem rather necessary. This would be the least preferred option and the data would need to be convincing. But of course we are not ruling out this and it could be well-justified that this is the only way forward. And in this case, the indication would be for the unmet need.

So at the end of the day, in terms of what the label will look like, what we are saying in our guidance document is that the indication in section 4.1 of the CMPC will read something like for the treatment of infection due to the specific pathogen -- let's say to the example before, Gram-negative aerobes -- in patients with limited treatment options. We referenced to section 4.4 and 5.1, which is the warning section and the section of pharmacodynamics

data.

Consideration should be given to official guidance on the appropriate use of antibacterial agents. And also, in section 4.2, we would state that it is recommended that the new agent should be used to treat patients that have limited treatment options only after consultation with a physician with appropriate experience in the management of infectious diseases, which would also lead to in the opinion to a status of restricted prescription medicinal product. And I think this is all. Thank you.

[Applause.]

DR. COX: Great. Thanks, Marco. And now, our next speaker is John Rex, from AstraZeneca. And as many folks know, John's been a thought leader in the area and done a lot of work and we're grateful for his willingness to join us today and all of his contributions to preparing for the workshop too. So thank you, John. The podium is yours.

DEVELOPING ANTIBACTERIAL DRUGS FOR UNMET NEED AND SO THAT WE STAY AHEAD OF THE EPIDEMIC: POINTS TO CONSIDER FOR DEVELOPERS

DR. REX: Thanks, Ed. And thanks to the organizers for the chance to be here. Am I loud enough in the back? It sounds okay to me. So these are my affiliations and my disclosures. If you know me at all, you know that I'm an internist who went into industry a little over a decade ago because I was seeing bacteria that I didn't know how to treat. And so, that's what I work on now. I'm going to cover several topics. They're somewhat orthogonal to each other and to the presentation's we've had today. But it will all come together into a clear message at the end: pathways for registration, economics, some common mistakes and some conclusions.

So pathways to registration -- there are five ideas that I'd like to be sure that you walk away understanding. I'm going to cover the first four in detail in my talk. Joe Larsen will pick up on the fifth one in his. Let me just now just start walking through them. The first topic has to do with language. And we've struggled for a long time with the problem that a year ago we finally sort of tumbled into a partial solution to, which is the problem that

we understand how to talk about MDR and XDR. We also understand the idea of wild type. But there's something in between wild type and MDR that's really important and that's the proposal is for a label called UDR -- usual drug resistance.

And what UDR means is that it's what you expect. It doesn't mean susceptible. It doesn't mean that it's susceptible to everything. So if I'm using a carbapenem as my comparator in a clinical trial, then UDR is anything that a carbapenem would cover. You know, and so it means I can study every kind of resistance but a carbapenem in a UDR's group. But are they really MDR? Well, it depends on your perspective. Okay, so that's the idea of UDR. UDR -- and the real implication is that in a clinical trial, I can pick a single blinded comparator that I can use globally comfortably.

When you get into MDR and XDR, the comparator just gets harder and it could be that XDR, there's no such thing as a single standard comparator. Every patient may need a different comparator. UDR and MDR and XDR are a sliding scale. So in 1940, when

penicillin was invented and active against S. aureus, S. aureus was UDR to penicillin. But then, MRSA emerged and then it was the DMR nightmare bug. In the 1960s, we found a lot of papers about the horror of MRSA and then vancomycin appears. And so, now it goes back to being UDR.

The other message is that if an organism is susceptible to the novel test agent, it's susceptible to the novel test agent. The response is independent of whether it is UDR, MDR, XDR to other drugs. Here's another way to see that. In theory, UDR is relatively common and XDR is relatively rare, if we're doing a good job. And the notion is that when it's UDR, I can pick a global comparator relatively easily and that the activity of the drug is independent of the other -- of its status relative to other drugs.

So with adequate PK, data in a UDR setting, which remember doesn't mean wildly susceptible, it could be resistant to lots of other things. But data in a UDR setting tells you a lot about how it's going to work even when it's susceptible to almost nothing else. But it only tells you how it's going to work on

the infection and that's an important thing to remember as well. People who have XDR or super XDR killer bugs often have had a lot of health care exposure for some reason. The antibiotic will not cure their cancer, motor vehicle accident-related trauma and whatever else they've got, their underlying immune deficiency. It can only cure an infection.

This matters because, as you're going to hear, it is much, much harder to do prospective, randomized registration quality studies in patients with infections due to MDR or XDR isolates than UDR. Our internal data is that it's at least twice as slow and twice as costly, if you can do it at all. A number of reasons -- you'll hear some of them today -- but I'm going to only mention some of the ones that I've seen most commonly. First, patients have to present at a study site, as referral is hard. Infections move rapidly. Therapy has to start now. And if you say -- if you call up your hospital administrator and say, I want to transfer somebody into my hospital that has the most resistant Klebsiella that anyone has ever seen in the world,

they're going to say, really?

And actually, sites work really hard to make those isolates rare, which is why your administrator is going to think you've gone daft. No site wants to be a center of MDR, XDR excellence. Think about that billboard in front of your hospital. So chasing MDR/XDR is really an exercise in Lasagna's law. For those of you who don't know him, Louis Lasagna was a pharmacologist who noted some years ago that the incidence of patient availability sharply decreases with a trial begins and returns to its original level as soon as that trial is completed. So the bottom line is we want MDR/XDR rates to be low. If it's easy to do a study in this space, we as a community have done something terribly wrong.

Number two, superiority versus non-inferiority. New antibiotics are going to be, and indeed must be mainly developed in a non-inferiority setting for comparison versus an existing agent in the setting of UDR pathways. But I say again, UDR doesn't mean susceptible to everything. It can be resistant to lots of things. It's just susceptible to the

comparator. The reason for this is that as a designer, I have to design my trial to actually avoid superiority. I cannot, should not and I will publicly shame anyone who seeks to enroll patients where we know that resistance is likely to the test or the comparator. That's not fair to the patient.

It's very unlikely to -- you're just not -- it's really rare to see superior efficacy over a fully dosed modern comparator when the pathway is susceptible to same. I mean, when the carbapenems work and you fully dose them, they're good drugs. It's very hard to be superior on toxicity. We're only treating for 10 to 14 days. You know, most tox signals take longer than that to develop. And again, MDR/XDR is rare, we hope. Superiority is a high stakes gamble for a novel agent. As Ed has said, you're testing the drug and the test. You could lose a drug because you gamble on this. If your primary aim is superiority and the study fails, that's it. You're done. The study result says failed. You cannot go forward. But if you see superiority by accident in a non-inferiority study or in a subset,

you can claim that result.

Simpler pathways, LPAD and tier B/C. We spend a lot of time discussing simpler ideas and there's a consensus and it makes sense that PK/PD-based dose selection should make it possible to register in somewhat smaller data sets. But actually doing this has turned out to be very hard. LPAD is an idea that was created for in the U.S. some legislation to kind of help with this about approval based on combinations of data plus some safeguards. But the bottom line is that LPAD really seems to be unlikely in the U.S. and it actually would have been only for the U.S. anyway.

And in fact, what we have now is a very practical implementation, as you have been hearing, about what -- of the tier B and tier C ideas that appeared a couple of years ago. And I'll say that the tier A, B, C, D nomenclature is not something that you will ever see in a guidance document. It's not needed but it is useful in presentations to have a feel for it along this pathway. It basically corresponds to example one and example two that you heard Marco and

Sumathi present.

So tier A is the classic setting where you can do two big trials. That's what we've always done. It's nice and easy. Tier D corresponds to this idea called the animal rule -- more discussion about that. But basically it's a setting where you can't do efficacy studies in man, like anthrax. I hope I can never do that trial. And then, in between, there are some stair steps. And the easiest way to explain B and C is to see some examples.

So here are hypothetical tier B and tier C drugs. Tier B is a drug that has a spectrum that covers an entire syndrome. You'd be happy using it as monotherapy for complicated intra-ab. So what you should do is one standard Phase III study of drug B versus a standard comparator at a standard body site. This will be focused on UDR pathogens, no super, super MDR/XDR. But if you choose your comparator well, you can cover a lot of resistance ground. This study will provide a crystal clear view on safety and efficacy of drug B. And then, you put with that a little study that's not pivotal. It gets as much as it gets. It's

an open label salvage study, might be randomized, might not, where you play go-fish for really, really hard pathogens and you acquire some data.

Tier C, this is a drug that is -- one version of this is a drug that's narrow spectrum, perhaps only one organism, perhaps only P. aeruginosa. What are you going to do here? Well, the problem is that P. aeruginosa, as we're going to discuss in great detail tomorrow, is a relatively uncommon pathogen. So here, because of that difficulty, the idea is you're going to do something prospective and randomized, the best you can, and you're going to be doing it versus whatever is the best available therapy for that drug which means it's almost certainly going to have to be open label. You may have to go to open body sites to get enough numbers. So you may end up with sort of this really small data set where no part of it individually is satisfactory. You might also run an open label salvage study where there's no best available therapy. And you might even do an observational study of inadvertent, ineffective therapy for the target pathogen that might estimate

placebo response if it's a pathogen that is so resistant that you do that. It might apply to Acinetobacter.

Forward -- am I doing something wrong? There we go. The good news is that tier B works. The guidance from the FDA and EMA, as you've clearly heard, both describe a tier B-like idea as entirely acceptable. The candidate must address unmet need and the label will include language in the form of patients with limited treatment options. It makes perfectly good sense. We're not yet there with tier C and that's the purpose from my chair of today and tomorrow is to sort of wrangle with this notion. And it's the problem of limited statistical testing. And you know, I can say that for the FDA it's a sticky point because there's a statutory requirement for substantial evidence based on adequate and well-controlled investigations. We heard from Marco that the EMA is willing to consider it. It's not entirely clear to me yet if it could be the only indication you've got, but maybe so.

But clearly they're using a language in the

form of treatment of infections due to x in situations where you can't gather much data. But let me say that, you know, if you phrase it as a regulatory issue, you're making a mistake. It isn't a regulatory issue. Actually it's an all of us issue. What do you as a doc want to know? Well, I want to see something that shows me that it gets to the site of action. I want to see something that shows me that it at least cures a few people. I want something. So in many ways, what you're seeing here is sort of an advanced declaration of what you as a doc are going to say about it when it hits your doorstep. So don't phrase this as a regulatory hurdle. I think that is a wrong way to look at it. Really what we have to come up with as a community is what's acceptable. You know, what's workable and don't make the perfect the enemy of the merely good.

So my practical transaction is that for a single pathogen, tier C drug, it's going to have to be non-inferiority. But you're going to have to make some -- do some wiggling around, and tomorrow you'll see some examples of that kind of wiggling around.

Build the largest data set you can at plausible body sites. Adjust some wide margins. Maybe do more than one experiment. Maybe triangulate on this thing. Look, superiority is always acceptable, but see above. I just think that's a very high risk gamble.

Pressing button, but nothing is happening. I have to wave my hands. Let's see. There must be another button. No? Yes? Would someone advance the slides for me? I'm going to retreat to that. Thank you. A little disambiguation, pathogen-focused. The phrase is tier C and pathogen-focused pathways can be confusing. I want to make it clear at least what I'm talking about. Here are the three ways you could read this language. Truly narrow, Acinetobacter only. Broad-spectrum, but includes a rare pathogen; or any spectrum, but you focus it on some subset of difficult bugs. Like it covers all the Enterobacteriaceae but you can also treat CRE.

When I talk about pathogen-focused pathways and I think most of the time when we're discussing it over the next day or two, we're really talking about number one in in this. It's so narrow that you don't

have the choices implicit in versions two or three of these conceptual drugs. Next slide. All right. The implications of some of this, and the future economics of antibiotics all collide. Next slide, please. So the current economic model for antibiotics is broken. The current approach is that we develop a new drug. Everyone is delighted to have the new drug. They clap you on the back and say, wow, that's fantastic. Thank you for doing all that hard work. Matter of fact, this is so important as a drug, we're not going to use it. And as a consequence, it's entirely rational -- stewardship, hold the drug back. You know, that's really what we as a community should do. It's what I did when I was a hospital epidemiologist.

From an economic perspective, of course, you've just spent $500 million bringing that drug to market and that's a financial loss. And many analyses show exactly the same thing. It is not -- it is irrational to start antibiotic R&D under the current development models. And the problem that underpins all this is that we have a basic -- what amounts to a pay per use model that reimburses for only one portion

of what an antibiotic does. Next slide, please. So I'd like you to think about antibiotics as the fire extinguishers of medicine or sometimes another way to think of them is think of them as the firemen of medicine, the firepersons of medicine, to be gender-neutral.

So think about fire extinguishers. They have two roles. One is to put out fires, obviously. But the other role is to make it safe to be in a large commercial building like this one. So how often have any of you used a fire extinguisher? I hope it's zero, except in training, which is kind of fun. But in real use, I hope zero. And yet, would you be happy to be in a building without a fire extinguisher? You haven't needed it all these years. Would you be happy to forego it? Think about the firemen down at the corner fire station, which isn't too far away. When should you pay the firemen? Per fire? No, obviously not. So if you think of antibiotics as being the fire extinguishers or the firemen of medicine, they have the same two uses. You use them to put out fire, but equally you use them to make it rational to go into

the hospital, get your hip replaced, get your cancer treated, take care of the premature baby, all those things that antibiotics make available so that every day you walk in and you look at the antibiotics on the shelf and you gaze at them lovingly and say, boy, I'm glad I'm not going to use that today but I'm glad it's up there.

Next slide. So the buzzword here is de-linkage and we have to find economic models that separate reward from usage. There's a big project going on in Europe called DRIVE-AB that's working on this idea, things like lump sum access fees, insurance-like models. In the United States, the presidential advisory council has taken up the charge to try to sort this out and I know that others in this room are very interested in this topic. Don't yet have an answer to this. But we have to find ways to pay for the value -- both values of the fire extinguisher.

Next slide. Now, there's an implication for the developers in the room. Fire extinguishers come in different categories and you actually need one of

each. If you've had fire training, you've learned that for paper, wood and plastic, you use certain kinds of fire extinguishers. But for electrical equipment, you use another kind. Antibiotics are much the same way. Incremental extensions of fire extinguishers are nice. This one's a little lighter or something, whatever. But that only gets you so far. The real value is when you create a kind of fire extinguisher for a category that doesn't yet have a fire extinguisher. So think about that. Strong scientific value, novelty in mechanism, lack of cross-resistance. This is the best way to get your fire extinguisher bought in the future.

Next slide. Some common mistakes, and so now I'm going to weave this back into some of the themes I've been pointing at. Next slide. So lack of dose justification. Paul Ambrose is about to give a talk on this that you're going to enjoy. But let me just say that my version of this history is you can't do too much. One animal model plus one isolate equals inadequate. You need clear data on the PD driver, clear data on the PD index magnitude, use those

preclinical data to conclusively rove you have a dose that gives the right exposure and then the last line, please, do not forget to prove that you can get that exposure in the target population. I got it right, Paul?

Next slide. Misreading regulatory feedback. For Phase I and Phase II studies, this is important to know that the agencies will only tell you to stop if you're likely to hurt somebody. You're free to use any endpoint you'd like for dose finding. You want to look at cytokines, you want to look at toenail color, anything you want. But acceptance of that exploratory endpoint does not endorse that endpoint for a pivotal trial. The other aspect of this is that following regulatory advice, as I heard someone once say, is an underused strategy. Go talk to the agencies. They really will make time to help you, and listen closely. It is very tempting to hear what you want to hear. We have all been guilty of this. I have definitely been guilty of this. Pay close attention when you hear the words sponsor risk. They see more stuff than any of us see. Listen closely.

Next slide. Unrealistic expectations, expecting superiority over a fully dosed comparator that is really pushed pharmacodynamically to its max. This better be rare and you must, must, must not deliberately enroll subjects whose infection is likely due to a comparator-resistant isolate, unless of course there are no other options. But then, in that case, it's Ebola and we've failed as a community. Also do not chase the really hard indications first. Yes, I know endocarditis would be a great indication to have. But you'd really better learn something about your drug in a more ordinary setting before you cast all of your fortunes on that very difficult pathway.

Next slide. I want to be labeled for the treatment of CRE. I want everybody to understand that that never happens. Instead, your drug will be indicated for the treatment of infection X caused by strains of Y that are susceptible to your drug. It won't say that are resistant to other drug and that's because, especially across compound classes, resistance to one drug doesn't have a one-to-one

linkage to susceptibility to another drug. So the fact that it -- the fact that it is resistant to a carbapenem, does it make it susceptible to your drug? No, of course not.

Next slide. Some conclusions. Next slide. So my key points. Seek novelty. Get it registered. Justify the dose. Lots of preclinical PK/PD data. If at all possible, do a standard non-inferiority study for a standard comparator versus a strong -- a standard indication versus the strongest comparator you can come up with because, remember, even though I'm calling that UDR, if you use a carbapenem, it can be R'd to everything but that carbapenem and that covers a lot of ground. Seek the super difficult bugs on the side. Don't make this pivotal. And finally, keep it simple. The required number of miracles should always be less than one. Thank you.

[Applause.]

DR. MARKS: Thank you, John, for that points-to-consider approach across a broad range of things. I especially like the fire extinguisher model. That seems to be evolving nicely as an

analogy. I think all of us keep looking for that dry chemical approach. But the organisms stay ahead of us. You also talked about the importance of PK/PD. So next, we're going to have Paul Ambrose, who's the president of the Institute for Clinical Pharmacodynamics, has some approaches in here which clearly outline and show the predictable failures and successes. The title of his talk is "Pharmacokinetic Considerations in Unmet Need Programs." Thank you, Paul.

PHARMACOKINETIC CONSIDERATIONS IN UNMET NEED PROGRAMS

DR. AMBROSE: Thank you. It's certainly my pleasure to be here today. Here are my disclosures. I'm happy to talk about those to anyone who cares. This doesn't advance? Advance. So I brought in my talk to pharmacometric considerations in programs of unmet medical need. I felt pharmacokinetics just too constraining. Next slide, please.

So let me start off by saying we haven't been doing a really good job at picking doses for our Phase III antibiotic development programs. And the

goal of my talk here today is to share with you a way of thinking so that we can do a better job in the future, right? And so, what's really critical to remember is that antibiotic development programs fail. It's loss often about bad drugs and much more often about bad decisions. And that's a really bold statement for me to get up here and say, but it's really true. Consider our place in drug development. As a group, we have participated in many, many of the drugs that have reached regulatory approval over the last decade or so and also some of the failures. And we've been behind the scenes looking at how decisions are made. And so, I think we have a perspective that not many people really have.

So from our perspective -- okay, advance, please. It's hard to do it without the slides. So a lot of folks in rooms like this really focus on superiority versus non-inferiority over time. That's what really the focus has been. And for me, that's an important question, but it's the wrong question. It's the less important question. The more important question is how do I ensure that my antibiotic is

dosed correctly so that the drug not only makes it through the regulatory process, but reaches the hands of clinicians and helps save patient lives. That's really the most important question. And I feel if we spent half of the time arguing about how to get the dose right as we've spent arguing about inferiority versus non-inferiority, I think by the end of today's presentation, you'll agree with me that we'd have more antibiotics on the market today to treat sick patients than we do at the moment.

So let me show you what I mean. Superiority can be found on an exposure-response function. So this is just a made-up drug. You see drug exposure is a logit function there. And you see the relationship between AUC to MIC ratio in response. The green data represents a dose of this drug, which happens to be three times the dose of the red dosing regimen. You can see the green regimen is up on the plateau of the exposure-response relationship and the red data -- the red distribution of patient exposures is down on the curve. The green regimen is superior to the red regimen, right? It's associated with a much better

probability of response than the red regimen. This is really what I'm talking about.

We need to push our doses up that exposure response curve. And the further you push them up the exposure-response curve, the harder it is to prove superiority, right? Right? More and more cures, fewer and fewer failures related to study drug. That's the result. And sadly, it's very rare that we actually do this in our clinical trials. But occasionally, we do. Most recently, The Medicines Company studied meropenem-vaborbactam, a brand new ß-lactamase inhibitor, a complicated urinary tract infection. You can go to the Web and see the results of that trial.

They enrolled hundreds of patients. How many failures? Four. Four failures. They optimized meropenem not only with dose but with duration of infusion. Four failures, or 1.6 percent. I'm not a statistician, but I'll tell you it's got to be thousands of patients to show superiority to that regimen, right? So the further we push up that dose-response curve, the harder it is to prove superiority.

Unfortunately, we don't often pick doses that sit on the plateau of our exposure-response functions. We pick them on the slope, in the middle of that slope and sometimes towards the bottom.

Next slide, please. So if my hypothesis is correct that this pharmacology underlies all of this stuff, right, our successes in drug development as well as our failures, then we should be able to predict our failures as well as our successes. So can we predict our failures? Yes, and right now, I'm going to take you to some uncomfortable places. Before we get on how to do it better, we're going to visit some uncomfortable places. We're going to go to those programs that failed. And by going there, my goal is not to point fingers at anybody in the audience or cast aspersions on anyone. My goal is to set the groundwork on how we can do this better in the future. So first, you have to believe -- first, I have to demonstrate for you so that you can believe that pharmacology underpins all of this stuff.

Next slide, please. So this is daptomycin and this is the exposure-response relationship for

daptomycin in the animal model. It happens to be the neutropenic mouse thigh infection model, the data generated by William Craig. And you can see AUC-to-MIC ratio is the PK/PD driver for daptomycin on the x-axis there and change in log10 CFU on the y-axis. And you can see as you drive exposure up, more and more bacterial killing. We all remember that daptomycin was studied versus ceftriaxone in patients with community-acquired pneumonia and we all remember that trial was stopped for lack of efficacy in the daptomycin arm. So let's take a look at that.

Next slide, please. The red distribution of AUC-to-MIC ratios is a simulation of the exposures in those patients. You can see the median, the 25th and 75th percentiles defined by the edges of the box and the bar and whisker plots for the range of data. You can see that the exposures lie -- wow, they lay on the bottom of the exposure-response curve. I'm sure Cubist thought they'd be near the top. But they sit near the bottom. Did they do this intentionally? And the answer is absolutely not. How did they pick their dose? They picked dose of 4 mg/kg.

But how? Well, it's the same dose they used in skin infections, where the dose worked. They also noted that they were much more active against pneumococcus than S. aureus. In fact, they were eightfold more active, right? And they had a couple of animal models. They had Bill Craig's mouse thigh model. They also had a hematogenous pneumonia model. But what they didn't have is they based their decisions on the wrong model. They didn't use the standard murine lung pneumonia model. Had they used that model, they would have seen the impact of binding to pulmonary surfactants in that animal model and they would have seen that it didn't work versus ceftriaxone in that animal model and they would have had the opportunity to abandon the program, even before it started. Instead, they executed that model post-mortem.

Next slide. So ladies and gentlemen, I think the daptomycin program was entirely predictable. Their fatal mistake was using the wrong animal model.

Next slide. What about tigecycline? This is again data from Dr. Bill Craig, set up identically

as before. As drug exposure goes up in the mice -- this happens to be Acinetobacter -- you see more and more bacterial killing. We all remember that tigecycline was studied in hospital-acquired and ventilator-associated pneumonia. Next slide. And it failed versus meropenem. Here are the observed exposures, the observed AUC-to-MIC ratios from these patients. You can see the median AUC-to-MIC ratio was just a little bit short of net bacteriostasis in the animals. And a large number of patients stretching with AUC-to-MIC ratios towards zero. Well, this can't be good, right? Tigecycline did not meet the criteria for non-inferiority. Why did they pick this dose? Why did Wyeth pick it? Well, they worked in skin infections. It worked in intra-abdominal infections and their sponsor perceived they had a safety concern. So they were going to go with the maximum predicted dose.

Well, next slide, their critical mistake in all this was the maximum tolerated dose was just insufficient, right? Don't go forward with a dose just because it's safe but your preclinical data might

suggest you've got a long way to go. So again, ladies and gentlemen, tigecycline's failure was completely predictable.

Next slide. What about ceftobiprole? This is again data from Dr. Craig, same as before. More drug in the mice, more time we see it in the mice, more effect for ceftobiprole. Next slide. Here's the distribution of time above MIC in patients treated with ceftobiprole. You can see they're not -- their median value is not even at stasis. Well, how did this happen, right? Well, in Dr. Craig's animal model, he noted -- he noted that the time above MIC needed for efficacy was the same in pneumonia and in thigh models which suggested that you were getting very strong lung penetration or very strong ELF penetration. In fact, some number approaching a hundred percent, right?

So what did the sponsor do wrong? Well, they elected -- they elected, against the counsel of their advisors, to do their ELF penetration study in people concurrently with their Phase III program. And why? The why was to save time. They were warned.

They were warned that penetration of cephalosporins into ELF is highly variable, going anywhere from 20 percent to a hundred percent. That was until they set a new low. Their drug penetrated 15 percent into ELF and this is the expected exposure distribution.

Next slide. It should be no surprise, ceftobiprole was predictable. But had they done their ELF study before launching their pneumonia programs, they would have had the opportunity to change dose, change interval or abandon the program altogether.

Next slide. Doripenem, again, exposure-response in the thighs of mice, data from Bill Craig again, same as before. You drive exposure up, good things happen. Doripenem was studied versus meropenem in ventilator-associated pneumonia. Let’s look at their exposures on the next slide. A little bit better here, right? The median exposure is associated with bacterial killing. But look at the variability and drug exposure at the dosing regimen study. It stretches towards zero. This isn’t good, right? You can’t have that many patients with exposures that stretch towards zero and expect that you’re going to

be approved. So again, next slide, their fatal mistake was not accounting for drug clearance. Increased drug clearance in VAP patients was just not accounted for in their dose regimen selection.

Next slide. So here we come to meropenem. These are data from, this time, George Drusano's laboratory and this is in mice. It's an ELF of mice. So it's an ammonia model this time. And as you drive time above MIC for meropenem up in the ELF of mice, you get more and more bacterial killing. Now let's look at meropenem. Next slide. Is it any wonder? This is a 2 g dose every eight hours with a standard infusion of meropenem. The median exposure is up on the plateau of the exposure-response relationship, as are most of the patients that would be simulated. Notice the variability of penetration into lung tissue. Very high. So you get that little tail that goes towards zero. But the vast majority of people sit up on top.

This, by the way, ladies and gentlemen, is why you should be thinking of combination therapy in patients with hospital-acquired pneumonia because you

will always have this subset of people with poor exposures down low. So combination therapy is the way to go. So this is what you want your drug -- if you're developing something for hospital-acquired pneumonia or ventilator-associated pneumonia -- this is what you want your drug to look like. You want it sitting up on top of the exposure-response curve, not halfway down, not at the bottom, but at the top if you want to do the best for patients and the best for your program. Next slide. So meropenem, it's predictable it would be successful. It's really clear why doctors used this drug so much and in such severely ill patients.

Next slide. So just in case you thought I may have cherry-picked and just picked those four drugs, I picked them because they were in ventilator and hospital-acquired pneumonia programs. These are data that we presented a few years back at ICAAC, when it was called ICAAC, and we looked at the probability of PK/PD target attainment based on Phase I data and microbiology data available at the time that doses were picked versus the probability of approval by the

U.S. FDA. You can see as the drug exposure goes up or the probability of target attainment goes up, so does the probability of approval. And there's a mix of HAP and VAP programs in this particular collection of studies. There are 20 studies involving 17 drugs, 14 failures and six successes.

So you might note that little red circle on the bottom, all the way towards 100 percent target attainment on the bottom. There are no guarantees. That drug happens to be garenoxacin. You might remember garenoxacin developed for community-acquired pneumonia. It failed, not because it had insufficient efficacy. It failed because it had safety issues. But there are no guarantees. But the further you drive your target attainment up, the better your chances are.

Next slide. So hopefully I've convinced you that failure is predictable and now we're going to answer the question, well, I've got my shiny new drug, how am I going to keep my NDA on track. Next slide. I think it's a proven approach and it's PK/PD embedded in your development program from the very beginning

with a very deep collection of animal studies, PK/PD in design. It's getting PK early and throughout your development program. It's learning at each step and reassessing your beliefs about your drug and adjusting dose as necessary. And if you do all those things, you'll succeed. But I can tell you that our problems are sometimes much more basic than that, and I'll point out two challenges that we see when we talk to sponsors we work with all the time.

The first one is, well Paul, we didn't work in the animal model. That's because our drug's got a unique mechanism of action. The laws of pharmacology don't apply to us. And they don't say it that way, but it's essentially what they're saying. Well, let me assure you I haven't seen an antibiotic yet that the laws of pharmacology simply don't apply. So if you're thinking that your drug is special, it's probably not. It really is just about killing bacteria. That's what it does. If it's not killing bacteria in the animals, you've got a big, big problem.

The second problem is people want

checklists. We all want checklists, right? And people, they feel good about checklists. They don't have to think. But I'm sorry, drug development requires thinking, right? I've got a checklist. I've got my MIC data. I've got my animal model. I've got my Monte Carlo simulation. I'm ready to start three, Phase III. No, you're not. Well, I don't want to do those studies, Paul. They're not required by the FDA. The EMA doesn't make me do them, so I don't want to do them. I can save time. Well, I hope I can show you in a little bit that this is a very foolish approach to drug development. It's actually very high risk.

Next slide. So let's start off with the MIC. Pathogen susceptibility, the patient population matters. These are data from Dr. Ron Jones. They were actually developed after the workshop that the FDA put on, on HAP/VAP a number of years back. But it's looking at the percent susceptible in patients with hospital-acquired pneumonia versus ventilator-associated pneumonia. And the first number is always hospital-acquired pneumonia, followed by, after the slash, ventilator-associated pneumonia. You notice

all of them bolded, many of them bolded. That's telling you that there's greater than 5 percent less susceptibility in the ventilator-associated pneumonia patients. So patients with ventilator-associated pneumonia oftentimes have higher MICs than those that don't. Now, this seems really obvious to any clinician that treats patients -- that treats patients. But I don't think we always fully appreciated this. This happens across pathogens.

Next slide. What about pharmacokinetics? Pharmacokinetics also differs on patient population. Many drugs are renally cleared. So here's creatinine clearance in 600 or so patients with hospital or ventilator-associated pneumonia. The red represents ventilator-associated pneumonia and the yellow or gold, hospital-acquired pneumonia. And you might notice that there's a cluster of patients. There's more red at higher creatinine clearance values. These patients -- the subpopulation of patients that are really pushing drug through their clearing organs, right? So they're getting rid of drug fast. That means there's low AUCs in these patients, right?

And there's certainly an ICU subpopulation that are hyper-clearers, right? People that have had motor vehicle accidents and so forth clear drugs very, very fast. So you have to account for these differences in clearance. And this may look subtle to you and those MIC shifts I showed you may look subtle to you. But they do make a difference. Consider the next slide. This I showed to you before. This is tigecycline in patients with hospital-acquired and ventilator-associated pneumonia. Next figure. This is those same patients stratified by whether they had ventilator-associated pneumonia or hospital-acquired pneumonia. The difference in the box plots, notice the hospital-acquired pneumonia patients did better, higher exposures than the ones with ventilator-associated pneumonia. In fact, if you remember the clinical trial, tigecycline did about as good as meropenem in patients with hospital-acquired pneumonia but really tanked in those patients with ventilator-associated pneumonia. I say it's no wonder. Look at the difference in MIC to AUC ratios in these patients.

Next slide. So as you're going through and

building your dose justification, I can't encourage you enough to pressure test your dosing regimens. A lot of sponsors, they just want to do that -- they just want to do that mouse study. They want to get their PK/PD target and that's it.

I encourage you to put into very challenging systems, like the hollow fiber infection model, where you can test your drug at high inocula, much higher than you can do in the -- generally do in the animals for long periods of time, certainly longer periods of time than you can do in any animal system and look at the relationship between drug exposure and resistance emergence on therapy. And select your doses, if you can -- if you've got this safety headroom to select your doses to shut that down, that'll increase the lifespan of the drug and increase your chances of success from an efficacy perspective in your clinical trials.

Next slide. So an NDA that arrives to the FDA on time but with empty boxcars is useless. People are in a really big hurry. They just want to get done as fast as possible. I mentioned before they want to

skip studies. If it's not required, I'm not doing it. Let's go, full bore ahead. I hope, again, to emphasize that this is a foolish proposition.

Next slide. Here's a typical Gantt chart that we see from some companies these days with these accelerated clinical programs. What do you see? Let's start off. You've got a SAD study, right, that they're probably doing ex-U.S. And then, when that finishes, they're going to file the NDA and they're going to tell the FDA the dose, right there. There's our dose, right? Well, what's wrong with that? You haven't done your MAD study yet. You haven't done your multiple dose study. You don't know if you've got nonlinear pharmacokinetics or any other pharmacokinetic issue. And by that time, you're filling your vials for your clinical trial already. You're blasting ahead. By the time you finally find out it's nonlinear pharmacokinetics, there's no way you're going to change your dose. You're going to say, well, we're already too far down the road. We're going to go. That's exactly what's going to happen.

And then look what else they do. They put

the BAL study, the epithelial lining study. They stack it right on top of the Phase III program. I already showed you how it's like running across the street and eventually you'll get hit by a bus if you run back and forth enough times. But this is exactly what we're seeing. And I also think most importantly, look at the time durations between steps. You don't see any time for thinking. Everybody's in a really big rush. No one's stopping, thinking, analyzing their data.

As a group that analyzes data for a living, I can tell you that people think that this is going to be done and you push a button and it's done in a week, right? It's not. Data analysis and looking at -- and letting data drive your decisions takes time. I think we all need to slow down and take a deep breath and make sure our studies are being done sequentially, in a way that makes sense. And concurrently, if we can -- if it makes sense to do, but just not race to the end because you could just be running off a cliff.

Next slide. So finally, a warning. Develop the drug you have, not the one you wish you had. You

know, when you hear people come up with their new drug, and you're laughing but it's true. Think of all the drugs out there. My drug treats resistant CRE, quinolone-resistant DAP, ß-lactam-resistant DAT. It works in lung, urine, feces, everywhere. It's wonderful. Come on. There's no drug like that. So you sell it to your investors on these false premises. You get a lot of money and it drives you to do really stupid things. So slow down, develop the drug you have, not the one you wish you had. And with that, nest slide, thank my colleagues who continue to inform my thinking. Thank you very much.

[Applause.]

DR. MARKS: All right. Thanks, Paul. Thanks for sharing your insights over your years working in the field. And now, I'd like to invite Joe Larsen up to the podium. Joe is the deputy director for BARDA, the Biomedical Advanced Research and Development Authority. And Joe's -- I'm sure probably everybody in the room is familiar with Joe. BARDA has played a very important role in the space of antibacterial drug development, both from the

standpoint of product development and also pushing forth the science in the field in general and looking at new and novel ways to develop new antibacterial drugs. And he's going to tell us a little bit more about that. Thanks for joining us here today, Joe.

BARDA'S MARKET RESEARCH FOR A CLINICAL TRIAL NETWORK FOR ANTIBIOTICS

DR. LARSEN: Thanks, Ed. And good morning, everybody. Can I get the next slide, please? So I'm an employee of the U.S. federal government. Uncle Sam has vetted me for any conflicts of interest. Next slide. So as Ed said, BARDA's been involved in antibacterial drug development since 2010. We basically form public-private partnerships for the development of new antibacterial drugs. We've been involved in one way or another in Phase III clinical trials for a number of the companies that we support, and we plan to be involved in Phase III clinical development of other -- with additional companies in the future.

Next slide. So the problem that we see with this is that every single time BARDA goes out to do a

clinical trial, it sets up that clinical trial de novo and pays for all -- to build and pay for all the infrastructure needed to conduct the trial each time we want to do one. So we wondered if there was a potential for efficiencies to be built into the system, perhaps through the development of a clinical trials network, to do regular registrational Phase III and Phase II clinical trials.

Next slide. So Ed already showed another diagram in his talk -- he stole a little bit of my thunder, that -- but his diagram I think, frankly, was a little bit better than mine -- but talks about the way that this would potentially work. And it would be that there would be a clinical trials network for a standard body site indication that would be continually running the standard -- enrolling the standard of care as the control arm in that trial. And then, over time, investigational products would be incorporated into the clinical trials network and compared to that common control arm. And this is a diagram -- a notional diagram of how this potentially would work.

Next slide. So as a first step in trying to understand this -- and this is a really great opportunity here to be speaking about this publicly because BARDA's perspective on this is that, A, we want to really hear from industry if this is something that people think is needed and would be helpful. B, we also want to understand from both a technical and cost perspective, you know, what this would cost and some of the challenges that would exist for us to be able to implement this. But we also want to hear from industry some things that we're not thinking about. And so, I'm going to highlight today other concerns and risks that have been brought up. But we are -- BARDA very much wants to hear from industry related to this to make sure that we're thinking about this in an appropriate way.

So when the government wants to understand something in the market, we do market research and we issue something called a request for information. And so, we issued a request for information on February 4th, received responses back on April 11th, and we received 11 responses, eight of which were through

standard CROs that gave us technical approach and cost data on how they would establish this network. And I'll share that information with you all today in a way that's been scrubbed for the individual responding companies. But we also received three responses from antibiotic developers, which were immensely helpful and those weren't providing technical or cost data. They were providing narratives of saying, hey, if you're -- if, BARDA, you're going to go forward with this, you need to be thinking about the following things. And that was extremely helpful to us. And again, this is something that we would encourage additional industry partners to come forward with and have that conversation with BARDA.

Next slide. So what did we assume? So we issued this request for information and we assumed a 10-year period of performance. We assumed there would be an initial setup period for about a year and that three investigational antibiotics would be brought in to the network and then compared to a common control arm. We sought information for complicated urinary tract infection, complicated intra-abdominal infection

and nosocomial pneumonia. We told the respondees that rough orders of magnitude -- we didn't need things down to a dollar and cent, but just to a general level of what they felt this would cost. And we bucketed it in two different kind of levels of patients, 500 patients and 1,000 patients for cUTI and cIAI and 3600 and 600 for HAP/VAP.

Next slide. So every single time you do something like this, you realize all of the things that you should have specifically asked for. And so, there's some important caveats to this information that need to be taken into consideration. And so, not everybody followed the instructions or provided the level of information that we would have liked. Indirect rates weren't provided in many different responses and that basically could increase cost by about 35 percent. Different responses use different assumptions in terms of how the network would work and what we were asking for. And investigator site costs were not included in certain responses and BARDA's clinical staff also felt that that would increase the cost by about 40 to 60 percent. So you're going to

see in a few minutes lower numbers. And then, at the end, I'm going to basically put out what we -- what BARDA thinks this entire endeavor would cost.

Next slide. So this is the summary of the various costs. And I've averaged them up and then I also provided the max and minimum values to give you a sense of the level of variability in the responses that we received. But in general, the average cost was about $20 million for cUTI, cIAI and HAP/VAP at the lower levels and then approximately, you know, $25 to $35 million for the thousand patient levels.

Next slide. Also we wanted to understand the cost of this, just to maintain the infrastructure. And so, we called that warm-based cost. That would be just having the network, just enroll the control arm so that it would be operational. And the mean cost there, it ranged a little bit by the number of patients people felt would be enrolled into the standard of care, was about $40 to $55 million with the maximum values being about $82 million and the minimum values being $22 million.

Next slide. Also, just to give you

additional sense as to some of the variability in the information that we received, this is the number of clinical trial sites, which I think is directly proportional to the cost that was reported out in the responses. One response thought that just 75 sites total would cover it. One respondee did not report the number of clinical trial sites that would be required. But on average, for the lower levels, it was about 100 to 125, 130 and for the larger bucket it was around -- basically around 175, 180 sites.

Next slide. So one of the questions that came in, in some of the responses from industry, was really a lot of questions about how this would be ran and who would govern this. And also, there was some questions related to if this could be adapted to drug-resistant pathogens exclusively to do those type of trials. And I think our opinion at this point is that if this was to go forward, it would focus on standard non-inferiority trials and not focus on resistant pathogens for all the reasons that I think we've heard today already.

We are envisioning that this would be an

ACRO that would be administering this. Some questions felt that -- they questioned who should lead this effort and some of the respondees felt that it should be led by a group of academic investigators. We were actually walking into this thinking that BARDA would actually lead this effort. But that's of course open for discussion as things evolve. And then there was the overall question of what would be the organizational structure. And I would say several of the CROs in the responses did provide an organizational structure and a governance structure as part of their proposals. But I think that's getting down to a level that's a little too deep for us to be presenting here in public.

Next slide. So what are the overarching challenges of setting something like this up? In my mind, the number one is financing, right? If we're going to build this infrastructure, it has to be maintained because ultimately if this is kind of -- ultimately, it would be an economic incentive for an antibacterial development because efficiencies will be built in by having a common control arm. But if

industry can't rely on that as a network as being there and being operational, then it's not a functional incentive.

I think initially in order to gain interest into a network like this, BARDA or other partner organizations would have to finance the clinical trials in its entirety to show that the network itself was competent and could actually execute. And then, over time, I could envision a model where we would then switch to a fee-for-service where companies would pay themselves to actually tap in and utilize the network. But of course, because of some of the efficiencies that would be realized, their clinical trial may be less experience or may be able to be done more rapidly.

One of the big questions we also have is that are there sufficient products in development to warrant this investment. There are not a lot of antibiotics in clinical development. And if you look down to the preclinical pipeline, I would not describe it as vibrant and robust. But nevertheless, I think there probably is enough to support standing up and

having a network. And once that network was also in place and operational and demonstrating to be competent, it may spur others to enter into the field to start doing antibacterial drug development because they saw that there was a favorable clinical landscape for development.

The big risk -- you know, the big risk for us is uncertainty, right? If we build it, will industry participate? Because the last thing I think any of us wants is what's going to end up being, you know, a several hundred-million-dollar white elephant. And so, it's going to need to be -- again, as I mentioned, we would have to pay probably for the first few drugs to go into this network to demonstrate its competence and then switch to a fee-for-service-type model.

Next slide. So just to be transparent in the responses from the three companies that responded -- and they cited a number of different challenges with this. And I would bifurcate those challenges into two buckets, one related to the protocol and how the trial would be designed utilizing a common

clinical protocol and the second being bucketed in terms of operational challenges of actually being able to run a network like this.

So there was a lot of questions about the flexibility of the master protocol itself and all of these questions were basically around how can I position my drug in the most favorable light related to the specific, you know, circumstances of my product, which are understandable. There were questions about how regulatory updates, auditing and compliance would be conducted. I would suggest that they would be conducted the same way for any other regular CRO. The selection of the standard of care was cited as being problematic.

One suggestion was to create a global standard of care map to suggest an aid to management. And they also submitted that getting sites to agree globally would be a significant challenge in the standard of care. Endpoint selection was cited as a challenge, also coordination between FDA and EMA was cited as a challenge and something that was needed to be addressed -- could be addressed perhaps through a

network like this. Questions over the data monitoring committees, whether it was the network or the sponsor that would be involved in this.

I mentioned again addressing product specific safety and efficacy objectives. Data blinding was a concern, how to handle dose adjustments. IV to oral switches was cited as a concern. And also, this last piece I think is really important and it is something that I don't think we thought heavily enough about when we put out this RFI, which was related to the handling of proprietary data. And basically, the construction of all the IT infrastructure that would be necessary to go into something like this we didn't even really put anything in there related to that. And the last thing that we would want to happen is a government-sponsored clinical trial network, you know, fumbles with some of the proprietary data and that would be a really quick way for anybody -- everybody to lose confidence in this type of incentive going forward.

Next slide. So after factoring in some of the variability that we received in our responses, I

would say the annual cost to establish this infrastructure is probably somewhere between $60 to $100 million annually. I think we probably would be comfortable subscribing about $75 million to -- and that accounts for the fact that some of these things doesn't account for startup costs or investor site costs.

If I were to finance this at a level that included standard of care in three investigational drugs to cover all of the risk and the things that we haven't thought about to date, I would think that this would need to be financed at a level of about $200 to $250 million per year. And I think that, you know, going forward, there's a number of key challenges that we're going to need to think through and discuss with our industry partners too before something like this would be implemented.

Next slide. So there are some alternative approaches that are being discussed and a lot of these discussions are going on in the EU. So you know, we asked for a large, standalone network to do registrational trials that would be functioning, you

know, explicitly on that. And the challenge there, in my mind, is one -- the most significant one to me is getting the level of financing required to actually be able to launch this. And the question is are there other models that could be examined that wouldn't require as big of a financial lift.

And there's some discussion in the EU with some folks that are suggesting that instead of building a gigantic, you know, standalone network, could you utilize existing networks and, you know, have them be governed in a common way, operating under I guess a common strategic network to be able to do this type of work without having to recreate the infrastructure. I don't know the answer to that. But I would say I think then the coordination of all of those different parties then becomes the challenge and I think those are equally challenging. There's also -- you know, I'm looking forward to the discussion about innovative clinical trial designs later today. Maybe that's the answer to some of this.

Next slide. So for next steps for us, we first need to think able to the pathway to financing

this. And there's currently a working group that's being ran out of the Wellcome Trust where we're having a lot of discussions on the protocol, the operational considerations and as well as the financing considerations and they're having a meeting in October where we're going to begin to discuss many of these things. And there's clearly other partners besides BARDA that are looking to try to finance something like this. And if we could all come together, it might be a much easier path to being able to finance something like this.

The information that we've received to date is very helpful. We'd be very open to receiving additional information from folks in industry because we really need -- if this is going to go forward, we need to begin to think about what a potential request for proposals would look like and the RFI was helpful in that regard, but I don't think we're all the way there yet. We need to continue to discuss and think about the ways that we can overcome the challenges that were provided to us and highlighted to us. And then, we also need to think about the most appropriate

governance structure to run something like this.

Next slide. So again, I just would say that we are very interested in hearing from industry related to this and would appreciate all of your feedback. My email and phone number is there. Don't hesitate to reach out to me if you want to discuss anything that I've presented today. Thank you.

[Applause.]

DR. MARKS: Thank you, Joe. I think a very fertile area for questions and conversation when we get back from break. We're thinking about maybe coming back from break around 11:20 and then add hopefully a few minutes onto your lunch break to facilitate interaction and dialogue among various stakeholders. So why don't we come back around 11:20? Sorry?

DR. COX: 10:50.

DR. MARKS: I'm sorry, 10:50. What did I say? 10:50, sorry. Yeah, why don't we do that, or come back around noon, you know? 10:50. Thank you very much, and we'll kick off with Ian, yeah.

[WHEREUPON, the foregoing went off the

record at 10:23 a.m., and went back on the record at 10:57 a.m.]

DR. MARKS: So we'll get started again very shortly. Thank you.

DR. COX: So maybe just to get started, one sort of logistical issue first. An ounce of prevention is worth a pound of cure. We found this behind the podium. If you're wondering what it is, it's a hotel card. So if people might just check their pockets, if somebody was up in the vicinity of the podium, if they're missing their hotel card, come to me and I will get it back to you so that you're not locked out of your room when you get back there.

DR. MARKS: All right. Thanks for --

DR. COX: If somebody doesn't have a hotel and they're interested in a hotel, come up and talk to me.

[Laughter.]

DR. COX: No, I'm kidding.

CLARIFYING QUESTIONS (PANELISTS AND AUDIENCE)

DR. MARKS: Thanks, everyone, for coming

back promptly. We're going to move into the questions section. And just taking moderator's prerogative, I thought I'd start off with the first one. We hear a lot about regulatory harmonization and the need for the U.S. and the EU to work together in terms of antimicrobial resistance. So I thought maybe Ed and Marco, you could share with us sort of what you do now, your thoughts about where this might go in the future, and if you could share that with us, start off with either -- Marco, you want to start first or --

DR. CAVALERI: Yeah. I think, as I said, in the context of TATFAR but also behind TATFAR itself in the recent years we had more and more chances of discussing the way forward on the development of new antibacterial agents between FDA and EMA. And also, we established regular contact with those, clear recommendation in the TATFAR set of recommendation around having a regular teleconference.

So what is happening is that every month we sit down for a conference between FDA and EMA in which we discuss development plans that have been proposed to both agencies or one agency but maybe with the

knowledge that the other agency will be involved later on in which we touch base around what is the current view of each agency with respect to the development plans and how much we can converge into finding, you know, a single, settled requirement for the developer, at least how we can define the boundaries around what can be acceptable and what not.

And I think this has really been important and efficient in, you know, cross-fertilizing the views between Europe and the U.S. and helping us in having a common understanding of the way forward but also of what would be the scientific basis and the evidentiary standards that would be required in both the regions. And maybe to add that we do recognize that in certain type of infection indication, we are requiring different primary endpoints.

And for the time being, we found a solution by way of different statistical analysis plan, which so far works very well and in deed there has not been a single case to our knowledge in which a company had to redo a pivotal clinical trial in order to satisfy the requirement of the FDA or the EMA. But save that,

I think we are putting efforts into looking into the future of building more rigorous scientific understanding of how to assess the benefit of an antibiotic and antibacterial agent in the context of this type of infection in order maybe to come up in the future with some primary endpoint that could be agreed by both agencies.

So it's a journey. But I think we are -- we understand the value of that and we are putting efforts in order to do the best we can to convert today and also with a view that in the future there might be more chances of converging once new ideas and new options for primary endpoints on how to design clinical trials in these types of infection and also for unmet need will come up. So I don't know, Ed --

DR. COX: Yeah. No, thanks, Marco. Very helpful and very complete. You know, just to sort of reiterate, so you're hearing the same thing from both folks. I mean, agreed TATFAR has been a helpful vehicle for us to interact. And as Marco said, you know, within TATFAR, I think the first version of that report, we noted that in fact the clinical trials that

are used in Europe are essentially, you know, the same clinical trials used here and if there's an instance where there's different endpoints, then we would find a way to make those clinical trials useful for both places by a different statistical analysis plan.

And as Marco's noted, we continue to work on the endpoints. And I think, you know, a number of folks in the room here today have been involved with the efforts through the FNIH to work on endpoints. And you know, we see this as an area where, you know, the science, you know, will essentially, you know, bring us to the set of options that, you know, we think will be, you know, helpful to the future and get us to a greater degree of common understanding because if the science is there, it should work really for both groups.

We also -- just to add a couple of things, we share guidance documents in development, which is helpful too so that we, you know, have both the scientific exchange and the opportunity to learn from each other. Similarly, with regards to development programs, we're sharing comments, you know, with each

other and also having, you know, the opportunity to discuss the comments. Sometimes the comments are very clear, but having that opportunity to talk with each other, you know, can be even more helpful.

We're able to do that under a confidentiality agreement and we do -- for those that choose to take sort of a formal approach, there is also parallel scientific advice that is available to those that do it. And we've done a few of those and worked with Marco and his group on that and very much, you know, appreciate those opportunities to work together in that formal approach when people choose to go that way. And maybe I'll stop there, but yeah.

DR. MARKS: Thank you, Ed and Marco. Maybe now we'll open it up to the panel for questions. Aaron?

MR. DANE: Yeah. So it's probably mainly for Marco and Sumathi, but partly for John in terms of the -- so when you were talking about when we get into the unmet need and the sample sizes are smaller, so clearly we can't do the traditional statistical criteria that we usually do and apply. Sometimes we

can still do something. But if we're in a situation where the numbers are even smaller than that and all of you outlined that, how do you see that data being used? Because I guess it's -- we get some data and then we've got to figure out when does it help us feel better and when does it concern us if we're only dealing with a handful of cases.

DR. CAVALERI: Yeah. I think it will have to be looked at on a case-by-case basis. I think it's very difficult to say this is the threshold. Below this number it will be impossible to draw conclusion about if we can do that because it will vary. And of course, here we're entering into a bit of uncharted territory in the sense that indeed we are talking about very small trial with a very heterogeneous population. And so, the interpretation of the data might be a challenge anyway. What we are trying to do is to come up with the idea that it will be challenging, but it will not be impossible.

And therefore we are opening to consider, in light of the unmet need and the potential benefit that would derive despite the uncertainties, it might still

be possible to draw a conclusion on a positive benefit-risk despite a data set that is very small. So yeah, I think it's difficult to reason in terms of absolute numbers here. And you know, each pathogen will have different considerations. The data may show something different. Of course, the PK/PD package is essential and that will be, as I said, one of the pillars of the evaluation of antibacterial agent in the context of this unmet medical need with limited clinical development.

DR. DUDLEY: Yeah. I think maybe along those lines of what Marco was talking about -- Paul, I'm going to kind of surprise you on this a little bit. Maybe you could talk a little bit about how the approaches that your group has taken, with taking smaller data sets and modeling exposure-response, which then does give an idea of the magnitude of treatment effect. And I'm thinking of some of the tigecycline work that you guys did a few years ago where you looked across the various exposures of tigecycline and were able to sort of quantify the treatment effect that was seen in a variety of

infections and whether that will help with these small data sets.

DR. AMBROSE: Sure. We did a couple of analyses, both involving tigecycline, but one of a more frequentist nature and one a more Bayesian in its thought process. And not surprisingly, with the frequentist approach, with an exposure-response relationship, your confidence bounds get really, really, really wide. And we were able to calculate sample sizes and they were quite large based on that approach.

But when we took a more Bayesian approach and we acknowledged -- we allowed some of the animal data to inform our exposure-response analyses of the clinical efficacy data, such as the direction of the exposure-response relationship, we were able to tighten those confidence bounds I think quite a bit that allowed for the calculation of a much smaller sample size with which to do those studies. So I think those things are possible to open to other statistical approaches. And it looks like by this agenda, we are.

MR. DANE: Yeah, and I think for me, it's -- just so I'm not misunderstood, I'm not thinking we need any statistical -- traditional statistical criteria. It's just that idea of assuming we rely more heavily on the PK/PD information, assuming we count all these other things, how are we going to use the data that we do generate, because it is difficult and it's just having that feel for what -- how are we going to react to whatever we see as we're trying to plan a study.

DR. COX: Sam, do you want to --

DR. BOZZETTE: -- change directions -- so John, I mean, your tier C drugs, it seems like there's going to be a mix, no matter what control arm you pick -- there's going to be a mix of organisms that are resistant and sensitive. So I'm wondering if you could say a little more on what those trials would look like. Do you need different control arms based on the sensitivities? Do you enroll people right away or do you wait until sensitivities are available, which unfortunately takes a while unless you have a molecular marker. Just what are those trials going to

look like?

DR. REX: So your first question was about a mixture of susceptible and resistant in the control arm, susceptible and resistant to the control comparator -- to the chosen comparator. And what I'd argue here is that you should -- there are very few organisms for which I can't design an active control arm. It's actually pretty rare right now, you know, which is good, okay? So in the most general case -- like tomorrow, we're going to discuss at some length a pseudomonas-specific drug. You know, most of the time, pseudomonas, if I put one -- I can pick one thing and probably put something else with it and it'd be pretty rare that my comparator regimen for that a pseudomonas would be inactive.

So in that circumstance actually, you know, my problem really is that pseudomonas is just not all that common as an organism. And so, I end up with relatively small numbers. And that actually leads -- so the question from just a moment ago where somebody said to Paul, can't -- well, if I use pharmacodynamics, can I prove to myself that the

magnitude of the effect size relate to placebo is larger, which will let me use a smaller study, right. The problem that you get into is let's pretend we actually say, well yeah, the effect size -- without a drug, it's -- you know, there's like an 80 percent M1.

So let's actually have a really big effect size and design a small trial. When you get down into groups of like -- the denominator's 50 and 50 on each side of the equation, the problem there is that if both are active and you're expecting them both to be active, then you have almost no wiggle room for a little bit of heterogeneity. We'll actually show that tomorrow, that a movement of one patient from success to failure can actually dramatically alter your view of the data set. So you don't get out of the box by arguing for a smaller data set. You get into another box. You get into another problem.

So the difference -- so you know, that's how I think about this. And so, different control arms, well, I'm not too fussed about it being -- if I do drug A -- tier C drug versus per patient design therapy, if every one of those patients is on active

therapy, I think that's actually perfectly fine because that's what you do in the real world anyway and I'm expecting them all to be good and I'm not expecting to beat that therapy. It's a little messier. They're going to be -- the AE profile stuff may be harder to interpret. But it doesn't both me that much, provided that you believe that most of the time the comparator was an active drug. I see that Paul wants to jump in on this.

DR. AMBROSE: Yeah, a little bit of sideways direction, like PK/PD often hits people. You can show pre-clinically in any number of models that it's not the resistant determinant that predicts efficacy. In other words, if you hit the right exposure, AUC-to-MIC is big enough, you kill the susceptible bug just like you kill the resistant bug. There's nothing magic about that. I can't think of examples at all where that relationship really begins to break down over clinically achievable relationships.

What's different in the patients with infected -- infected with MDR or XDR is a different

patient population. They're often much sicker and there are other comorbidities or other reasons they're dying. But again, as John pointed out, you can't do much about that. So to me, optimize your dose and I'm less concerned with the numbers of patients you have in XDR or MDR study, as long as you've already demonstrated that it's drug exposure that matters, not its label.

DR. COX: Maybe another question for Paul. So Paul, just in follow-up to your presentation, you were talking about patients who have low exposure to a particular drug, arguing for, you know, maybe going in with a couple of drugs. And I'm wondering can the patient that -- you know, your thoughts on predicting the patient who's likely to have a low exposure to a particular drug and I didn't know if you were suggesting, you know, doing a TDM or just sampling a level. And then, beyond that too, if you do have a drug that, you know, the patient's got a low exposure, should you keep the drug around? Should you stop the drug? Thoughts on that? And then, if you're going to pick a second drug, how do you avoid having the same

problem with the second drug, you know, if this is a patient characteristic that they're clearing the drug a little more quickly? If you pick a second drug that's maybe not -- that's secreted similarly or has a similar metabolic profile. So any other thoughts on that? I thought that --

DR. AMBROSE: Sure, and you'll probably have to remind me of some of the questions that I miss in that list of them. But to start off with the first one, I think which is am I talking about needing TDM because of variability in drug exposure. Well, certainly if your drug's got unpredictable clearance, TDM long-term is a useful thing. But the reality is I think the outcome of an infection is dictated by early drug exposures. That first 48 or 72 hours, I think all doctors all instinctively know this.

And so, it's really important to have the right dose up front and that means pushing the drug exposure. We're not really going to have that much time for TDM. The event window's too short. It's not like HIV where we're going to be treating for years and we can move the drug concentrations up and down at

will, right? It happens all too fast. So especially for, you know, pseudomonas pneumonia, where half the patients that are going to die are dead within the first 48 hours or so. So to me, it's pushing that exposure up front. I won't argue against TDM for certain drugs. But I would push back and say pushing dose is probably your safer bet.

The second question was --

DR. COX: Can you predict who's going to have these problems?

DR. AMBROSE: Yeah. You know, if it's a renally cleared drug, that's your first hint. So if you've got someone that's really hyperdynamic, they might be a patient that's very high creatinine clearances, they might be a patient that's going to be at risk. It'll be simple things like that. And oftentimes our doses are not selected to cover those patients, right? We start with normal renal function and we kind of match our AUCs going downward into various renal function categories in a downward direction. But we don't go in an upward direction. So maybe that's something that we could think of.

And the second -- the last one I think was a question related to if you've got a drug that's got variable exposure, what is it that you do. You stop the drug or try to add something else. I think you put them on the drug that has probably the least variability that you can get to that has a dose that can account for that variability, number one. And number two, in some effect sites, like the meropenem slide I showed, I think that's really important for everyone to recognize there was this tail of exposures that approached zero, even with this close to pharmacodynamically optimized drug and why. And that's the high variability and penetration into the lung.

So the only way to overcome that is protect that fraction of patients as a second drug. You may have to begin to think about inhalation as an alternative route, you know, breaking on through from the other side. But I'm not aware of any data where people have two drugs into a patient, measure the ELF and see where varying levels of penetration of drug A influence drug B at all. I don't think any of that

data even exists. So at this point, you know, I think that's an open field. But I think that data is a clear argument for combination therapy in some indications.

DR. COX: Ian?

DR. FRIEDLAND: I had a question for Sumathi and maybe Marco can also answer this. Of those different study designs that you outlined, can you give us some indication of which of those -- you know, maybe in order of frequency, which of those responses actually have undertaken? You know, so have people actually done nested superiority trials? Are people doing superiority trials? Are people doing external control trials, for example?

DR. NAMBIAR: The vast majority really have been non-inferiority trials. There's been one person, maybe two who've attempted to do superiority trials. But really the vast majority is non-inferiority. We really have not used external controls. We haven't seen a lot of proposals for external controls. We've used external controls more recently in the context of an anti-fungal drug that was approved over a year ago.

But I think the vast majority are non-inferiority trials. And for Gram-negatives, it's usually intra-abdominal and UTI, either or both. HAP/VAP typically has been the second indication, which I think makes sense. I think, you know, you at least have the evidence that it works among the other body sites. And those trials are certainly a lot easier to do than a HAP/VAP trial. So most of the HAP/VAP programs have been the second indication that people use.

DR. COX: Marco, anything to add? You're seeing a lot of the same programs we're seeing, so I'm guessing it's fairly similar, but --

DR. CAVALERI: Yes. It's fairly similar. Of course we're seeing some proposals around MDR pathogens and in novel approaches as we were proposing in the addendum. But I agree with Sumathi the majority are still in the non-inferiority.

DR. COX: And Nick?

DR. KARTSONIS: Yeah. I had sort of a follow-up question to the non-inferiority question to Sumathi, which is now that sponsors have come with

these non-inferiority margins, have there been situations where you've allowed a wider margin? And if so, can you give us some guidance in terms of what a wider margin means?

DR. NAMBIAR: I was hoping that wouldn't come up. But yes, we have -- we have allowed wider non-inferiority margins and I think some of that information is available in the public domain. So there's no secret here. I think particularly we've done it in the context of complicated urinary tract infections. We've allowed for a non-inferiority -- I mean, traditionally it would be 10 percent.

But in an unmet need program, we've allowed up to 15 [percent]. But I think the important point is that we need an adequate justification for why you think the product meets an unmet need. It's not just a question of widening the margin because someone wants to get the trial done in a shorter period of time. And I think more recently, I think Ed and I keep saying there are many flavors of unmet need.

More and more we are seeing people, you know, make -- it'll be a very tiny incremental benefit

and they'll say, here, I'm able to address an unmet need and the answer to that is no. We're not willing to. I think you also have to keep in mind safety concerns. So widening the non-inferiority margin, getting a smaller sample size might be one solution to the problem.

But we do come across products where you've seen a safety signal and in that instance, you know, a smaller program is not appropriate. So it's less about the number. I think a lot of it really depends on what the drug has to offer and whom you are trying to study. So and for HAP/VAP, again, we have allowed margins of up to 12.5 [percent] that we consider as wider margin and programs that do such trials will have a limited use statement in labeling.

DR. COX: Aaron? Yeah.

MR. DANE: Yeah, again, it's a follow-on to a comment you made around external controls, where I can see, particularly in the resistant pathogen area, that there really isn't any data out there to be able to use. But I mean, what's your view on using external controls if you're in one of the body site-

type approaches, and there are recent clinical trials that could be used in that way? So is that something that you would be amenable to doing? Because that could make trials a lot more feasible if that control arm data could be used across the trial in that way.

DR. COX: I'd welcome thoughts from other people on this. But you know, for non-inferiority trials, I mean, people have been successfully doing those in a variety of different areas. So I mean, I don't think there's any tremendous barrier to doing that. I mean, you know, we do see as we look across trial to trial, we do see variation. And I guess the question is are you reducing or increasing variability or, you know, what is the comparability of the external control compared to the patients that are actually in the trial.

And you know, when people do external controls, I mean, we talk about the importance of, you know, having a protocol that would essentially enroll patients in the externa control that would be, you know, similar to the trial that you had been enrolling the test drug patients into. So there's a lot of

things to think about. But, you know, ICH E10 talks about historical controls and some of the issues around them.

So you know, trying to overcome those and, you know, one of the topics that's come up too in the context of the clinical trial network discussion would be is this would sort of be an ideal sandbox to try and work through these issues because there's an opportunity to have the same protocol in place over a period of time and really try and examine and explore what's really going on. You know, are the patients behaving, you know, sufficiently similar with regards to outcome when a similar protocol is applied. It'd be interesting to see that, how do things change. A new drug gets approved. It might change the standard of care. Does that change what we see and how do we figure all that in? So probably more questions to your question than answers, but --

MR. DANE: Well, no --

DR. COX: -- I think those issues are, you know -- are out there.

MR. DANE: I mean, in the meantime, that's

what I was thinking, is that, you know, if we've got relatively recent trials, that's closer to that network, if you like, is that, you know, rather than having to rely on something from 20, 30-plus years ago, if we can say, well, these trials were conducted fairly recently and the designs were sufficiently similar and we'd have to go through all that, does that allow that information to be used, which then reduces the burden on the future studies.

DR. COX: Yeah. Yeah, I mean, if you -- I mean, if you look at, you know, trial A was in these sites, trial B was in those sites and maybe the patients are somewhat different as you move from site to site, so the reason that the numbers are different is not just, you know, variability but in fact patient differences. So it's -- you know, and then, you know, we see protocols and oftentimes there are subtle differences or differences that exist within, you know, the definition of what a success is.

And you know, that can change your numbers significantly. So when you look at historical reports in the literature for outcomes for particular disease

conditions, and then you look at the results of the clinical trial, because of the way the endpoint was defined in the clinical trial, it can lead to, you know, in some instances, markedly different numbers. So you know, it's a question of are you really apples to apples or are you apples to oranges. And if you are apples to oranges, why is that?

So I think there is still, you know, some work to be done there. And I know -- I'm thinking of, you know, the endocarditis trial and the definitions in the literature with regard to successful endocarditis and the definitions -- the first success within the clinical trial for dapto, for right-sided -- or for bacteremia, I should say, you know, really led to some fairly different numbers. And so, there's a lot to sort through in that. It's not just --

MR. DANE: So it's possible. But it would be difficult and there'd be a lot of steps to go through I guess is the --

DR. COX: Well, I mean, I guess -- I mean, you can think about, you know, what is the problem you're trying to solve and how big is the problem.

And if you're able to do, you know, well-done non-inferiority trials, I mean, you know, go forth. If there are issues that you're trying to solve and there are -- you know, we'll talk about areas where it's particularly difficult to do clinical trials and it may be worth looking into this a little bit more and trying to figure things out because you'll take a problem that's insolvable and make it, you know, solvable.

So you know, I think it's important to think about the nature of the problem and where solutions are, you know, most helpful and most needed and, you know, try and work through it. So does that help, Aaron?

MR. DANE: Yeah, and that's a good point. So I'm thinking of the situation where it might be possible to recruit maybe a couple hundred, but no more. So you're halfway between a really small development program and the fully powered one. And it might allow you to do a different randomization ratio or something like that. So this wasn't the idea of you just have an uncontrolled study you'd compare it

with. You'd have some reference across the two that you'd compare. But just trying to make those sorts of situations more feasible, to get something that would support approval.

DR. COX: Yeah, and I think we really will venture into that area tomorrow, where it is very difficult to actually get the patients to get to a powered study. So I'm sure we'll be talking about that more tomorrow. So Helen, did you want to add something?

DR. BOUCHER: I'll just comment to add to your point, Ed, about the difficulty in the bacteremia trial. And I think that there are a couple of issues that we've already talked about. One goes back to John Rex's comment about the movement of small numbers. You know, that was a trial of a small number of patients and there was heterogeneity, right? We had different people in different buckets of diagnoses. And that was something that had to be accepted to do that, to really try to complete that trial.

At the end of the day, I think that one of

the things that was most helpful was that there was a group of patients that all the patients were well-characterized, but there was a group of patients in whom their bad outcome was indisputable where there was some treatment effect. And I think that that was, at least sort of our perception of how a conclusion of success could be made.

And so, somehow in this discussion of if you're going to have a small group, whether it's with a wide margin or no margin, including patients, at least some patients in whom it's unequivocal that there's impact of drug is helpful. And I think that was at play in the antifungals back in 2001 and back in 2014 and Nick Kartsonis and I were there in 2001. You know, so that notion is I think one we can all agree on.

I think the challenging part comes in to what about the trials where we don't have those patients, and there's still a need? You know, there's still a need for an oral drug to treat ESBL UTIs. And as the clinician who deals with this all the time, I don't want to forget that we just don't have people

with HAP/VAP. We also have young, otherwise healthy people who have to come and get a PIC line for their ESBL UTI and they have a need as well.

DR. MARKS: Dennis, you wanted to make a comment?

DR. DIXON: Just wanted to echo a comment made by John Rex on the importance of speaking to the regulatory agency early and having a dialogue and a discussion to learn the way forward. That also applies to funding agencies like NIH and BARDA. And your comment, John, that there is a strong temptation to hear what you want to hear, we see that too. And so, I think people take the encouraging words and they don’t look so much at the sentences or comments that start with but, however and whereas and that’s just so important to understand the reality in moving forward.

And just to comment, I think it was a really good idea to have this workshop and to have this discussion openly so that companies out there can start to learn from others and can get a sense on what they might want to bring forward to you and have an early discussion about.

DR. MARKS: So we might -- before we go to Tom, we might just invite if there are people in the audience that have a clarifying question, just make your way to the microphone and we'll get to you right after Tom.

DR. LOUIS: Just quickly to highlight something both implicit but somewhat explicit in Paul's presentation and that is that the delivered dose isn't a number. It's a distribution and that really I would push for distributional thinking on almost everything. In this case, the biologic effect is really the integral of that uncertainty distribution over, in this case, a nonlinear curve and things could either be much better than you think or much worse than you think. But in either direction, it's best to keep that uncertainty throughout the whole system. I know that's harder than putting down a number. But you'll have much better assessments and better trial designs and no magical cure, but at least a sort of strategic approach.

SESSION 2: REAL WORLD EXPERIENCES IN CONDUCTING SUCH TRIALS

DR. MARKS: Any clarifying questions from the audience? I was just checking to see. Hi, over here? Any questions from the audience? Okay. Is that okay? All right, well, with that, we'll move on to session two, real-world experiences in conducting such trials. And great to have Ian Friedland, chief medical officer from Achaogen. His talk is "Developing Antibacterial Drugs for Patients with Unmet Need: Experience and Recommendations." Thank you, Ian.

DEVELOPING ANTIBACTERIAL DRUGS FOR PATIENTS WITH UNMET NEED: EXPERIENCE AND RECOMMENDATIONS

DR. FRIEDLAND: Good morning, everyone. And I'd really like to start off by thanking the FDA for inviting us here to come and share our experiences enrolling an unmet need-type study. So I'm going to go through some of these positions and give you the basis for the positions in my talk. I'm going to talk a bit about the feasibility or actually rather the infeasibility of conducting fully powered trials, given the low number of available enrollable patients.

And nonetheless, despite the difficulties of enrolling these types of trials, the data that one can obtain are critical and provide really important data to clinicians. These smaller data sets can be highly descriptive and they can support exposure-response analyses. But it is imperative that data in this unmet need population, including outcomes, is integrated in some shape or form in the product label.

So why even conduct these unmet need studies? We can just do a standard UTI II indication, get the drug approved. And this slide highlights the big differences between the standard population, say for cUTI, complicated urinary tract infection, acute pyelonephritis, versus a typical unmet need study, the one that I'll be describing today, which is blood stream infection and hospital-acquired/ventilator-associated pneumonia due to carbapenem-resistant Enterobacteriaceae. The standard UTI study does not directly address an unmet need, where clearly if you focus on unmet need, that's going to address that particular population. In UTI, patients have few comorbidities. There's low mortality rates, whereas

in the unmet need population, there are significant comorbidities, high mortality rates, multi-organ failure, very, very different patient population.

Duration of therapy could be different. Doses could be different. The pathogens are clearly different. John Rex referred to UDR. So it's a standard UTI trial has usual drug resistance. This could include something like 15 to 20 percent extended spectrum ß-lactamases. It's very unlikely you're going to see carbapenem-resistant enteric. Polymicrobial infections are usually excluded, whereas in the unmet need study, they're all, by definition, multidrug-resistant. We do see extremely drug-resistant and even pan-drug-resistant strains. And polymicrobial infections are common. PK is very different in the two populations. UTI looks a lot similar to Phase I-type populations, whereas in the unmet need population, the PK is much less predictable. There's much less variation. Significant changes in volume of distribution. And in our particular instance, we're studying our drug as a single agent for UTI, but in combination in the unmet

need population. So one gets very different information.

So plazomicin is a new aminoglycoside that Achaogen is developing and this drug has broad activity against Enterobacteriaceae, including strains resistant to other classes like carbapenems. And you can see there on the top line, the activity, the minimum inhibitory concentration, 50 and 90 of plazomicin showing potent activity against this collection of CRE isolates, in contrast with a group of other commonly used antibiotics. All the values in red are resistant, with only a few that have some activity, shown in blue.

So this is the basis of our Phase III program. We have two Phase III trials. Our cUTI trial, called EPIC, is the basis for registration. That's the trial that we believe will give us approval through the FDA and EMA. The CARE study, which is our study in carbapenem-resistant Enterobacteriaceae, is providing additional support of data. It's a smaller randomized trial. Originally we started with just the CARE study. But later, as that study went on, it

became clearer that enrollment was going to be challenging. We introduced the UTI study as an easier path to approval. Both studies are expected to conclude later this year and support a filing in the second half of 2017.

So let's go back to the beginning and look at our original CARE study design. And this was originally designed as a randomized, open-label superiority trial in patients with bloodstream infections and ventilated pneumonia due to CRE. This was -- this is a comparative trial versus colistin. The treatment arm is plazomicin in combination with either meropenem or tigecycline, so a combination regimen. Comparator arm is the same combination, but using colistin this time.

Primary endpoint, 28-day all-cause mortality and we were planning on demonstrating superiority over the colistin regimen. And this was based on a meta-analysis at the time showing a 35 percent mortality in patients treated with colistin. And with a 12 percent absolute reduction in mortality, we would have 78 percent power with the sample size we calculated. We

did get a concession from FDA to do the one-sided alpha of 0.05. The total sample size calculated assuming an 80 percent evaluability was 360 patients.

So this was the original feasibility done by our CRO. They did a very detailed exploration at many sites around the world looking at incidence of CRE. And this is the summary they came up with. In nine countries, using 68 sites, in these nine countries, they projected we could enroll 115 patients per year, which would mean the study would take -- 360 would take three, three-and-a-half years to conduct. As it turned out, the only country which approached the original prediction was Greece, and we can maybe talk a little bit later about why Greece managed and why the rest of the world struggled with this kind of trial.

Early on in the study, we -- when the study was going slowly, we looked at some of our metrics and we looked at the number of patients that we prescreened and by prescreened here, I mean patients haven't signed consent yet. And you can see of the almost 700 patients who were originally screened, only

14 patients were eligible for enrollment in the trial. And here are some of the reasons why patients were not eligible. Science could not prove that it was a CRE and, very importantly, patients exceeded the 72 hours of prior antibody therapy that we allowed in the study. Other important exclusions are things like low APACHE scores, polymicrobial infections and, very importantly, emerging colistin resistance that occurred during the conduct of this trial.

If we look at this on a more granular level, this is the experience from one of our good sites in Greece, showing that they definitely did see carbapenem-resistant Klebsiella in their hospital. And this is a detailed analysis, 17 patients that they looked at with carbapenem-resistant Klebsiella. Importantly, none were in ICU and this is important because most of our investigators are intensivists. But out of the 17 patients they looked at, only two could be enrolled and there are the reasons why patients were excluded -- low APACHE scores, resistance to colistin. So you can see that even though these infections are fairly common, these kinds

of exclusions are very difficult to predict up front.

Because of the slow enrollment, we implemented two major amendments to the study. The first one, we tried to loosen or broaden the entry criteria for the randomized cohort. So we allowed all hospital-associated pneumonias to be enrolled. We clarified some of the definitions of pneumonia. And we also added slightly different endpoint. Instead of just doing mortality, we did so-called mortality-plus, which is mortality plus other significant disease-related complications which are more closely related to the primary infection. Despite these changes, we saw minimal impact of this amendment.

So we then introduced a second amendment and the second amendment actually introduced a totally new cohort and this was a single arm, plazomicin treatment arm in which all the patients who were not eligible for the randomized cohort could come into that cohort and still get treated with plazomicin. And this included now patients with urinary tract infection who were excluded from the randomized cohort, lower APACHE scores and importantly are things like colistin

resistance, which was not allowed in the randomized cohort because colistin was the comparator.

And this is a snapshot of enrollment. This graph is not necessarily to scale. But you can see the original projection of 360 patients and our actual enrollment is tracking far short of that prediction. You can see where we introduced cohort two, which was the single-arm plazomicin treatment arm that did result in a bump up of enrollment. Unfortunately, the randomized cohort still tracks quite a lot below that.

So what have we learned from our experience in the CARE study? The site surveys that CROs perform -- I think a lot of us do know this -- grossly overestimated patient enrollment. Of all our sites, only a small subset, maybe 15, 20 percent, actually enrolled more than one patient. Superiority studies like this would only be feasible if many sites in countries have a CRE incidence similar to Greece. And those of you who know what the situation in Greece is, their carbapenem-resistance rate in Klebsiella runs about 80, 85 percent in ICUs. And clearly we don't want that situation to emerge in the rest of the world

before we can conduct these kinds of trials.

There are -- the barriers to enrollment actually evolved during the trial. For example, resistance to colistin became more and more of a problem as the study went on. Site engagement is critical. These are difficult trials. The VSCAs [ph] get easily discouraged. We spend a lot of time talking to our sites, doing site engagement activities. The studies are expensive. And in this instance, BARDA's support for this trial was essential for a small company like us to conduct a trial like this.

But if we are going to undertake these studies, and we do believe one can get extremely useful and important information, it is critical that somehow this information does get included in the label to ensure that the information is available to prescribers. And here I'm talking about even efficacy data in this unmet need population. This is in the context of we do actually have proven efficacy in the usual population. It will be a smaller data set. It will have uncertainty. But I think the nature of the

data set, the uncertainty can be highlighted in the label. The PK is very different in these populations. The microbiology can be very different. I think it's a given that we would include safety information in a different population like this. And this may be the only source of information on combination therapy.

So this is just highlighting how different the populations are in terms of PK. And the basis for this is largely differences in renal function. This is a renally excreted drug. And you can see a very broad range of renal function that we see in our CARE study in comparison to our EPIC study, our cUTI study, and what we'd estimated from population PK modeling, which is based on Phase I and Phase II. And you can see on the Phase I/Phase II, our UTI study, we get mostly normal, mild and moderate renal dysfunction. But in CARE, now we start seeing substantial numbers of patients with hyperclearance, which we know it's this population in particular that has caused problems in the past. We also get a substantial number of patients with severe renal failures, including those who are on continuous renal replacement treatment. So

a very different experience. It's very difficult to design Phase I or Phase II or UTI studies that can capture this kind of variability. Also interestingly, because of this extreme variability, we do get a whole range of exposures, which does make this data set very rich for doing exposure-response analyses.

The microbiology is also unique in the unmet need population. Yes, in our UTI study, it is focused on Enterobacteriaceae. Yes, we do see multi-drug-resistant enterics like ESBLs. We do see aminoglycoside enterics. But the CARE study is where we get carbapenem-resistant strains, colistin-resistant carbapenem strains, tigecycline-resistant. So kinds of resistance mechanisms and patients with these infections that you can't get in other kinds of trials. Also, we do get patients with higher MICs and this collection of these organisms with high MICs will help provide a more robust breakpoint assessment. And we also see bacterial species, maybe a little less important. But usual UTI is E. coli and this is focused on CRE. So it's mostly Klebsiella.

In conclusion, it's infeasible to conduct

rigorous inferential trials in these kinds of unmet need populations. And here, I'm referring to carbapenem-resistant enterics, resistant Pseudomonas populations, Acinetobacter-type studies. But these studies do provide really important and interesting information that's critical for clinicians to make treatment decisions. It is imperative, though, that these data do get included in the product label. And I think we would all agree that if the regulatory path was really clear, the studies in the unmet need population would be more likely to be undertaken and funded.

This is a last word, if I can get the slide to move. Thank you. My thoughts based on our experience in what are considerations one needs to take into account in thinking about viable study designs in this unmet need population. We do need to think what we can do with small studies, try and make them more efficient. So let's first start with rather than start with theoretical study design, let's start with what's feasible and look at this is possibly the population we can enroll and what can we do with this

number.

So these kinds of studies, to me what's feasible is somewhere between 40 and 80 patients, definitely less than a hundred. And the question is if you've got that number of patients, what can you do with that? We can definitely look at different endpoints, and I think we are working with CTTI and FNIH on more sensitive endpoints for things like HABP/VABP. Because of the small number of patients, I believe we should aim to get all or nearly all the patients on your study drug, which would then mean that we need to get control data somewhere else. So either external controls, shared controls and here is where I actually think a trial network could be very useful helping us get control data in this unmet need population.

Clearly designs that allow early institution of study therapy are very important. Our CARE study requires the confirmation of a carbapenem-resistant Enterobacteriaceae. That can take three or four days. To me, that misses the whole opportunity for drugs to be started early, to show their true potential. So if

we can't come up with study designs where you can use study therapy early, or at least as early as possible, I think we've missed the opportunity to really test the true drug effect. And obviously here rapid diagnostics can help. I do think we are going to have to think of pathways that incorporate combination therapy as a sort of definite simplifier, trial designs that will allow us to treat polymicrobial infections, which are common, that will allow us to start therapy earlier. And lastly, I do fully appreciate and definitely want to encourage the harmonization between FDA and EMA because clearly it is a barrier to sponsors when the two agencies have slightly different approaches. And thank you for your attention.

[Applause.]

DR. COX: Thanks, Ian. We appreciate you sharing your experiences and your insight. I think it's helpful to the field in general, and your willingness to present to the group on that is greatly appreciated. So now, I'd like to welcome Mike Dudley to the podium. Mike is the senior vice president and

head of R&D at The Medicines Company. And he'll be talking with us about planning and executing a carbapenem/ß-lactamase inhibitor program focused on treatment of KPC-producing CREs. Thanks for joining us, Mike.

PLANNING AND EXECUTING A CARBAPENEM/ß-LACTAMASE INHIBITOR PROGRAM FOCUSED ON TREATMENT OF KPC-PRODUCING CRE

DR. DUDLEY: Yeah. Thanks, Ed. And thanks to you and your colleagues for putting this program on. I think that all of us in industry are appreciative of what the regulatory bodies have done to really advance this field forward. My disclosures are here. And what I'm going to talk about is really starting from the beginning of what our thinking was as we designed this program from really the chemist bench and then moving all the way through design of a Phase III program. And it was around actually in the 2008-2009 timeframe when many of us were sitting listening to the spread of KPC-producing CRE in New York City that we regarded this as -- even before CDC -- as an emergent urgent threat that was going to be

facing healthcare institutions. It truly was a tipping point when one was now seeing resistance in Enterobacteriaceae, the most common infections in the hospital, to a very effective class of drugs known as the carbapenems.

So in terms of doing that, we went to the laboratory and designed then a program that was going to culminate in a new class of ß-lactamase inhibitor based upon a Pharmacophore [ph] which microbiologists knew about in terms of boronic acids of inhibiting serine carbapenemase -- serine ß-lactamases and optimized it then to be used for inhibiting the KPC enzyme. Secondly, we really wanted to work very carefully on optimizing its properties to work in combination with the carbapenem antibiotic. And this program advanced from literally the chemist benchtop to completion of enrollment in a pivotal Phase III trial in only six years. And largely a lot of that was because of the support of BARDA and many other partnerships that we've had throughout the year of being able to move this program forward.

Now, we optimized it for a carbapenem

because we recognized then that we could make use of the potency of a carbapenem antibiotic against Enterobacteriaceae and in contrast to cephalosporin combinations, which would then be subject to so-called usual drug resistance of ESBLs, we really focused then on a program that was going to optimize the molecule for inhibiting serine carbapenemases. And you see that evidenced here when you look at a very multi-drug-resistant or XDR-resistant panel, as shown on the bottom of the slide there, by double-digit MIC90s. Within this panel, 70 percent of these strains are inhibited by less than or equal to 0.6 µg/mL of meropenem in the presence of 4 µg/mL of vaborbactam.

The second piece that we did too though, and being mindful of the other part of this, is the pharmacokinetics. And we wanted to ensure a couple of things. One was is that we could match the pharmacokinetics of the partner ß-lactam -- here, meropenem -- with the ß-lactamase inhibitor vaborbactam, both within plasma as well as within epithelial lining fluid. And we accomplished that. We saw evidence of that in nonclinical models and then

this work done by Keith Rodvold published last year shows that in fact the penetration into ELF is very, very high, of course known for meropenem, when given by a three-hour infusion, but also comparably for vaborbactam as well. So well-matched microbiology, well-matched pharmacology to move forward.

It was then what do you do then in terms of designing a Phase III program to go forward with this. And Ian has covered many of the things -- and others have covered many of the considerations that we had here as well because we felt with a program that had been very mindful from the beginning of focusing on the pathogen and the infections where the pathogen was going to be found, we wanted to make sure then that we would have a Phase III program that would really reflect and translate a lot of that thinking that had taken place within the nonclinical and the early clinical development.

So I would just add also not only understanding exposure-response relationships within patients, understanding pharmacokinetics in special patient populations and safety as well. One other

issue which I would refer you to is the nice work from ICPD that actually with tigecycline that also uncovered also effect modifiers, both with respect to the patient's protein status as measured by albumin and how it modulated the exposure-response relationship in both HAP as well as VAP patients as well.

But also, I think, as we've talked about, it's important to inform clinicians about the results -- all the results that occur in Phase III programs in these patient populations. And I would draw your attention to even though we were thinking about this, a very fine viewpoint that Brad Spellberg and colleagues published earlier this year, that where they pointed out that for most drugs that are developed, the appropriate use in the clinic does in fact mirror the way that the drug was proven to be effective and safe in clinical trials. And so, a trial that also is involving these types of patients that Ian and I are talking about is also going to empower stewardship going forward because we want to provide information for clinicians in terms of

defining those indications and uses in that treatment population of patients.

So indeed, it's a novel idea. How about studying a drug designed for CRE in patients with CRE infection? And that's what we did. We came up with two trials. It's the TANGO program, TANGO I and II. TANGO I was indeed a guidance-directed both with EMA as well as FDA study looking at complicated urinary tract infections in acute pyelonephritis where CRE are indeed frequently found. So we rejected the idea of going, for example, to intra-abdominal infections because you don't see CRE infections generally in the usual population of complicated intra-abdominal infections. Our comparator was piperacillin and tazobactam. We recently announced the completion and the results of that trial where non-inferiority was indeed shown in the primary analysis population with indeed superiority also shown within that primary analysis population and in the primary endpoint.

Now, TANGO II is a pathogen-focused study, as you've heard about there. It was a study then that was designed to go into those patient populations,

particularly the complicated urinary tract infections, HABP and VABP and also bloodstream infections where patients had known or expected CRE. We designed it to be a 2:1 randomization so that we -- to get more exposures again in these patient populations with CRE, with meropenem and vaborbactam and that study is ongoing. And here's where kind of we -- more detail in terms of how we ended up with this. These patients are randomized, as I mentioned, 2:1 to receive meropenem-vaborbactam or best available therapy for 7 to 14 days. These are patients with either known or suspected CRE, as shown on the slide here, with a diagnosis of infection sites that I mentioned earlier. It is an open-label design, as you might expect, with the best available therapy arm, although we've done quite a bit here to try to reduce bias by having blinded investigators and adjudication committees, where needed, that we added as an amended protocol. And we used pre-specified outcomes I think much like what Ian was getting at here in terms of cure rates within these patients with meropenem and vaborbactam.

Now, I want to move though in terms of what

we -- sort of in planning this trial, what did we have to begin to think about. Well, one is what is best available therapy for CRE infections. And these are a number of retrospective studies that appeared in the literature here, with some of the learnings from those studies as well. It's certainly that, I think to Ed's point earlier, that carbapenems appear to have some treatment effect, even in this setting of resistance as well. But there are a variety of other factors that were identified retrospectively in these studies.

So what we did do though is in planning this trial and ultimately executing it was that we actually went forward to the sites that were actually -- many of the sites that were going to actually participate in the TANGO II trial to generate retrospective data from those institutions about outcomes and best available therapy, so somewhat of an external control approach, but more importantly, to really -- to teach us about what these patients actually had, how were they treated and how could we design the protocol then to optimize their enrollment within the study as well. And so, Elizabeth Alexander and Jeff Loutit and other

colleagues in our group that led this analysis did this study in these 22 major medical centers, both in the U.S. and Italy, again in Europe -- many of which, of course, would be sites in the TANGO II study.

And here's what we found. And we found, perhaps not surprisingly, what we know now is that many of these patients have comorbidities that would usually result in an exclusion from the typical registration trial. So as you scan down this list here, you can see that many of these patients were immunocompromised, about a quarter of them. Many of them had prior transplantation as part of it, chronic renal insufficiency, septic shock and APACHE scores with the means somewhere in the 20s.

So again, these are very, very sick patients, oftentimes not the ones that are going to be currently enrolled in typical registration trials. These are the primary endpoint which we were collecting, of course, which included mortality as well as other factors as well. Overall mortality, around 28 percent in all these. But note that 18 percent mortality even in patients who had UTIs and

acute pyelonephritis. Again, not typical of the types of patients that you're going to be enrolling with a UTI or acute pyelonephritis study and the typical registration trial as well. Many of these patients spent many, many days related to their CRE infection in the intensive care unit. As well, many of these patients being hospitalized certainly related to their index CRE infection for weeks at a time.

Now, what about best available therapy? What did we learn about that? Well, not surprisingly, the percentage here of non-susceptibility among existing antibiotics was pretty high. Quinolone's up to 90 percent. Even colistin/polymyxin B, up to 25 percent of them were non-susceptible based upon in vitro susceptibility testing. Now, probably one of the -- I was trying to figure out how do I summarize all this in terms of the therapies that we saw. And we saw everything from one-drug to four-drug therapies with about two-thirds of patients either getting mono therapy or three-drug therapy. But there was actually 69 different directed therapy antimicrobial regimens, okay? Sixty-nine different regimens involving one to

four drugs as part of that. I'd say that's not much of a consensus in terms of what you have and what you're going to get in these trials because of differential susceptibilities is lots of variability in what the control regimens are going to be.

So how did this help us then design the trial that ended up as being TANGO II? And the team worked then to really expect the enrollment. Our experience was not unlike that which Ian recounted for you is that a lot of these patients were getting knocked out based upon the usual types of exclusion criteria. So allowing immunocompromised patients, including those with prior organ -- solid organ transplants, those patients even on hemodialysis as well as have severe renal disease and also liver disease. And then, as shown there kind of in the fine print, which is always the dreaded language that knocks out a lot of patients with life threatening diseases with all sorts of medical complications, we changed that to simply be those patients broadly defined as having life threatening diseases with the subject needs to be surviving more than 72 hours from

randomization.

Well, finally, let me make a -- it's like one of those things, Joe, if you've ever asked for comments, be careful what you wish for. So let me make a few comments about a couple of things in terms of clinical trial networks and so forth as we sort of reflect upon this experience. We believe that the clinical trial network discussion is a really helpful one right now. But we believe that those are mostly going to be useful studying patients with resistant pathogens like CRE. We don't think that that's going to be very helpful with doing networks of registration trials such as in complicated urinary tract infections and intra-abdominal infections. We already know how to do those trials.

I'm not convinced that there's going to be much cost savings by being able to cycle through those. I think that the clinical trial networks and public funding for that should be used to help us solve the tough problems, not just saving cost should be the driver here. But it needs to be helping us to solve the problems. And one of the problems that we

had of course for us was trying to -- could we use rapid diagnostics, susceptibilities, resistance testing programs within the context of a trial. That would be very helpful to have within a trial network. Help us identify which of those 69 regimens might be the best available therapy regimen to carry forward that would be helpful for that. Then that would serve as a basis for evaluation of these new agents.

And of course strategies for managing these patients as well. And I think Ian would probably join me in saying we're kind of battle-worn going through this. And again, if this were part of a -- our experience was part of a network, it would have been nice to have this experience preserved in some way such that we can be able to get the kind of information that I think we all would like to see as part of our -- as part of our experience carrying forward in these patients.

Lastly, I'll add our voice as well to the idea that communicating the experience in these patient populations and pathogens is of interest, from a modeling standpoint as well as from descriptive

information, with the modeling approaches that we've touched on and heard about earlier as well. And I recognize that there are differences between Europe and the U.S. with respect to this. I know the Code of Federal Regulations is very specific about this. And I would just simply say if we need the CFR changed, let's change it so that we can be able to communicate this information to clinicians as well.

So just in summary, what I think we would all add here is that, very similar to the points made earlier, is that don't expect these clinical trials in these patients with pathogens of interest is to really yield the same information as guidance-directed registration trials. Absolutely agree that these non-inferiority trial approaches are really good ones for us to really get the pivotal information. But you need to get information I think in the target patient population. That really helps us to really understand these drugs. You don't do these for inferential testing. I think others have made that point very well this morning as well.

We can use these studies and the

information, particularly using PK/PD bridges to get us there. So information from larger clinical trials can of course be informative for interpreting these trials as well. And we would say that these studies are difficult. There's no question. But they're important. They're enrollable. And I think that we need to look at ways that we can basically be able to make these trials happen here and figure out ways to have these in the product labeling.

And finally, I'd like to thank my colleagues, particularly Jeff Loutit, Elizabeth Alexander and others that participated in the TANGO II and the 506 natural history study investigations. These are hard things. And I'd also like to thank BARDA for their ongoing support. Thank you.

[Applause.]

CLARIFYING QUESTIONS (PANELISTS AND AUDIENCE)

DR. COX: Thank you, Mike. Now, we'll move over to a brief clarifying questions for the panelists. And Joe, I might just ask one clarifying question from you. Thinking back, just help me

remember what you were thinking in terms of the clinical trial network and the focus. Was it on the non-inferiority trial designs or was it for the drug-resistant or was it for both?

DR. LARSEN: It was for non-inferiority standard clinical trials. And it was more about streamlining the fact that we have to pay to establish the infrastructure to do these trials each time we do it.

DR. BOUCHER: So I wanted to just ask a question or follow-up about the clinical trial network because I thought there was some -- that part of the reason that we didn't have more U.S. participation in a lot of these trials had to do with the fact that a lot of academic centers aren't sort of up to speed with doing high quality registration-type trials in a reproducibly high quality and efficient way and that part of the rationale for this network was to do that because we know we have the patients.

But many of us in academia aren't participants in industry trial and I think it's because -- it's not necessarily because we don't want

to be. It's because we don't necessarily meet the criteria. We don't perform well enough and as an academic I can sort of say that. So one idea of having a trial like Joe is outlining is that people would be up to speed. They'd have an infrastructure to be enrolling patients with whichever indication, whether it's intra-abdominal, UTI -- I mean, they're slightly different actually.

But if we had that kind of infrastructure going, if we had down to the study coordinators - we weren't always renting one for each study -- that that would make it more efficient and I think certainly a global desire would be to include more of those patients. So I just would love to hear from Ian and Mike a little bit more about thoughts.

DR. MARKS: So maybe we'll go from John to Dennis and then we'll come back and see if Ian and Mike have additional comments.

DR. REX: So to pick up on the theme about the trial network and then segue a little bit, the -- you know, Mike, you're right. We do know how to do complicated UTI studies. But at the same time, every

time we do one, even though I know how to do it, there's always the six-month ramp-up. You always have to go out and train all the sites. It takes time to get going. And that time lag is just a function of how fast you can roll it out. One of the fundamental ideas behind the UDR-focused network was that the network would be on constantly. The sites -- and at your site, every time you see an intra-ab, you think, trial network. And maybe they're only going to get randomized to meropenem because that's the only active drug. But you're actually paying for a clinical trial coordinator. The system is up and running and you bring a new drug in and it's instantly on at a hundred sites that are already enrolling. And so, the notion is it's almost an instant-on and instant-off of the drug that gets dropped into the system.

There's a paper that's going to come out in Clinical Infectious Diseases in a couple of weeks. Anthony McDonald, the first author, is an economist with whom I worked and we actually model it -- average 40 percent cost and time savings, if you actually get one of these networks up and running. So it's not

that we don't know how to do it. It's that we -- there's an inherent inefficiency -- every company has to build a one-off trial network to do its program. and that just takes time to turn on and turn off. So that's the trick.

So but a question for the agencies. Listening to these comments about the harder one, particularly Ian's slide about how different the EPIC -- different the two groups were in terms of renal function, it made me think this is the same problem we have in pediatrics where what we have is the difficulty with it's an unusual patient group, if you will. They're relatively harder to get at. And yet, we would very much like to be enabled to use the drug in that setting.

And the evolution of our thinking in infectives is moving from I'd like to have an efficacy study in two-month-olds with your new drug, which people would say, I'll do that, and then five years later you couldn't do it, to just give me the PK data to tell me how do I dose it in a neonate, how do I dose it in a four-month-old. Could it be that we need

to take a page out of the idea of the evolution of the thinking about pediatrics and say maybe that's kind of what we're trying to do here, is tell me how to dose it in, you know, fill in the name of, you know, a goofy subset.

DR. COX: Yeah. No, a good point is the -- you know, as the talks have been going on and we've been looking at the PK results and seeing some of the differences in the two groups, you know, it does seem like a very valuable piece of information that can be gathered from these different patient populations. I kind of hinted at this just briefly in my talk to the issue of generalizability if we are doing, you know, NI studies because they are feasible and that's where you can study, you know, the safety and the efficacy of a drug in a population where you can enroll a fair number of patients.

If the trial and patients with more highly resistant organisms is one where it's just simply hard to find the patients. It's hard to enroll. Then it does seem like, you know, gathering PK data from that patient population could be particularly informative

and could help to, you know, understand better how to use that drug in that patient population. And if it's, you know, a more abbreviated program focused on unmet need, it seems like that's an important piece of information in essence to bridge over to that population, if you will.

The other thing to think about too is that is there a way within the NI trials because I don't think it's the resistance phenotype per se that's driving, you know, the question about generalizability here. I think it's more, you know, who are these patients with regards to their comorbidities and all the other factors. So to the extent that you can understand that, whether that be in the patients that are enrolled in the NI trial because you seek out patients that are sicker or have greater numbers of comorbidities, that may also help to bridge the gap to some extent too.

DR. MARKS: So before we go to Dennis, just quick from Marco. Then we'll go to Dennis and then back to Mike.

DR. CAVALERI: Yeah. Just to add to what Ed

was saying, I think, yeah, indeed this is an important aspect. And I would like also to come back to what Paul was saying this morning. We are asking developers to consider straightaway if the new antibiotic is for unmet need and we'll be using the ICU to generate PK data in those patient populations because we know that there is an increased renal clearance. And we want to see the data and the target attainment there.

So it's pretty clear that we are demanding this data and it will be very important and would bring up, you know, important information from the standpoint of what could be the activity in this patient population. And pediatrics, as you may know, we started working on an addendum of our guidance. And indeed, one of the options that we were looking to is how much we can use PK data in order to support extrapolation to the various pediatric age groups.

DR. COX: Yeah, and one more quick point too. I think it may have been in Ian's talk. He talked about how, you know, the exclusion criteria essentially -- you know, that the patients wouldn't

get into the NI trial. I mean, that gives good reason I think for us to look back at the exclusion criteria for the NI trial because we probably shouldn't be excluding those patients. We should be getting them into the trial because, you know, we need to know how the drug works in that group of patients too.

DR. MARKS: So, Dennis?

DR. DIXON: Just to speak to Helen's point about the being up to speed or not in the United States, and I'll limit my comments to a very special subset of trials, not the usual registrational trial and network but rather the public health questions of resistant pathogens, be there Enterobacteriaceae or non-Enterobacteriaceae for carbapenem resistance. And with our experience on one large PK study, observational, and one large -- so large in that case was 150 -- large in the randomized control trial with colistin alone versus colistin plus the carbapenem would be over 400.

The primary factor was the density of infections at the site. And so, quality was not an issue in the preponderance of the United States sites.

We enrolled zero to one subjects per year at most of them. Closed those sites, added international sites and now we have a subset that are enrolling three to five subjects per month. And we have come up with this concept of alignment of networks rather than building one we can't afford in the beginning. And the alignment is our contract-based trial on carbapenem alone -- colistin alone versus carbapenem, we're aligning with COMBACT. And we have the hope of adding up to 10 sites in the next two years that could enroll in that range.

And on paper, if we find those sites, we will complete the study. How many times do things work out exactly -- within three years or so. But we know that time could tell otherwise on that. So it wasn't the quality, but it was the absolute incidence of infection, going to places like Greece and other places in Europe to find those places through census and site assessment and retrospective analysis of the subjects relative to the exclusion criteria look like they would work. So that's what we're hoping to do. And we also had an all carbapenem study to -- in our

colistin study to expand the definition of pneumonia because the subjects were not meeting the pre-specified criteria. We've modified that to be more liberal to improve our numbers.

DR. MARKS: So we'll go to Mike. We'll give Ian an opportunity. And if you have questions in the audience, if you'd just make your way to the microphones, we'll get to you next as we head towards lunch.

DR. DUDLEY: Yeah. Let me just kind of elaborate on a couple of things that John and Helen have mentioned as well. And I'm sensitive to the idea of the time lag that it may take. I think there's a couple of responses to that. One is we're actually quite aware right now, since we've stopped enrollment at our UTI trials, that another company has been able to come in and make very, very good use of that infrastructure through a CRO. So I guess I would say that a healthy clinical trials environment, which is what CROs were designed to do in the first place, was to basically set up networks where you could do trials like these is probably what you need.

We've gone through somewhat of a nuclear winter over the last decade with not a lot of development. So a lot of the stuff has had to be put together from scratch. But at least we're more than one program where they haven't experienced much of a time lag at all and been able to sort of tack on top of that.

Secondly, I don't think clinical trial network is going to solve some of the fundamental problems that we have in that. And Helen, to your point, it's not so much a quality issue. It's an issue now that oftentimes, for example, the Stop Sepsis campaigns that say you've got to have antibiotics in within 24 hours really work against that. Most of the clinical trials that are done now in urinary tract and intra-abdominal infections, particularly in urinary tract infections, are done ex-U.S. Infectious disease clinicians aren't interested in doing urinary tract infection studies in a normally healthy population of patients that are in that; same thing with intra-abdominal infections.

So you know, we're talking about usually

different people who want to do those trials. Most of the trials -- our experience was the same as others', that most of the urinary tract infection patients are enrolled ex-U.S. And I don't think a clinical trial network is going to solve all that as well. I think that what we -- what we -- if we're going to put some resource against that, I would say that let's try to get infectious disease clinicians that are struggling with CRE and other multi-drug or XDR-resistant infections engaged by a trial network that's going to be talking about getting information in those patient populations. And I think let's help the CRO industry do what they're good at doing and setting up trials and having a vibrant pipeline that will make use of that.

DR. MARKS: So thanks, Mike. So we'll go to Helen quickly. We'll finish with Ian, unless Dan had something -- so Ian and Dan. Then we'll take lunch. How about that?

DR. BOUCHER: Yeah. So just really quickly, I hear you on all fronts. And certainly no one's more enthusiastic about studying CRE than I am. But we've

heard from a lot of IDSA members and people in LLG and other groups that people in America -- infectious disease physicians in America aren't interested in studying in a Phase III way these infections, but find it incredibly difficult with the academic sort of structure, when you don't have infrastructure to be running a trial and you can't have a coordinator all the time because you don't have a budget. And this up and down is just not tenable for folks.

But you know, there is an interest and I think for our patients, it really matters. But from the IDSA perspective, you know, it's worth figuring this out. And I think to Joe's earlier point, you know, if this network was functioning, we could learn a lot of other things about natural history of this disease, about diagnostics, about, you know, even other drugs that might not be being developed by a sponsor, but that might be useful to take off the shelf. And we haven't even touched that subject. But I think again just to sort of make sure we don't kill this too quickly, I think that there are some other potential benefits. And at some level, it still

troubles me as a doc to think that I'm going to be giving my patients drugs that are developed 80 percent ex-U.S. when we have patients here who have these infections.

DR. MARKS: So, Ian?

DR. FRIEDLAND: So I'm going to echo a lot of what Mike was saying. I definitely do take what John is saying in that having a little bit more efficient, shorter start times is valuable to sponsors. But we can actually run UTI II trials, yes. Money would be -- having funding would be good and if you give us the funding, we can run those trials. We can't run them that well in the U.S. Helen's exactly right. And it's for other reasons -- they may be the ones that you think of. For example, UTI -- U.S. investigators will not treat on an IV drug for seven days. So we actually can't enroll those patients in the U.S. But in other countries, that's their standard of care.

So I think there are lots of reasons why the U.S. goes -- it's not just lack of experience of the U.S. investigators. But where we do struggle is

exactly where Mike Dudley referred to, is if we're setting up these unmet need populations, different kind of populations, we don't know enough about them to really design efficient trials upfront. And then, we learn as we're conducting the trial of all the errors we made. It makes much more sense that we first do the research up front, learn about the population, learn about the inclusions/exclusions and then we can design the trials more efficiently. And that's where I think something like a network could be very useful, gathering that kind of information for us before actually conduct the trials.

DR. MARKS: Thanks, Ian. Dan, and then we'll come back.

DR. RUBIN: So, first I want to thank the two groups for conducting trials in this very difficult area, in the patients with greatest need. I just have two clarifying questions for Dr. Friedland. First, could you talk a little about what, if any, difficulties the availability of ceftazidime-avibactam during your trial had on your ability to randomize to a colistin-based comparator and whether that was any

factor in the enrollment challenges? And then secondly, you mentioned the issues with emerging colistin resistance and the fact that those patients had to be excluded due to the colistin-based comparator regimen. I was wondering wouldn't that emergence of colistin resistance actually make it easier to show a difference or superiority, if not using -- if using a best available-type therapy regimen in your analysis for the future. Thanks.

DR. MARKS: So maybe we do it this way, because we have an hour right after lunch and this discussion -- ponder that over a sandwich or whatever. But I did want to get a quick comment from Sam, and then we'll come back. And Dan, if you'll remind us of that right at the very beginning, then we'll get to you. Is that okay? Thank you. Sam?

DR. BOZZETTE: I want to quickly pick up on what Helen and Mike were saying and point out that there are additional benefits to having clinical trials networks that are, you know, external -- externalities, if you will -- external to the conduct of the trial itself. You often increase quality of

care and you develop a cadre of clinical trialists and experts in the field. I think that's what happened with the AIDS clinical trials groups, for example. That's worked very well and essentially the whole notion of the HIV physician came out of that effort.

DR. MARKS: Thank you. Okay. No questions from the audience. So why don't we adjourn? We'll come back -- since I got the time wrong last time, let me look --

DR. COX: At 1 o'clock?

DR. MARKS: At 1 o'clock. Thanks very much.

[WHEREUPON, the foregoing went off the record at 12:21 p.m., and went back on the record at 1:09 p.m.]

PANEL DISCUSSION 2

DR. COX: -- we'll start in about one minute. I'll make a trip outside in just a sec just to bring folks in if we don't all sort of manage to get in here.

DR. MARKS: All right. Let's go ahead and get started for the panel discussion. I think where we left off was Dan was going to restate is question,

and then we were going to hear from Ian and Mike, at least. Dan?

DR. RUBIN: Thanks. So the two questions that were addressed to Dr. Friedland, but anyone else can chime in, were on the availability of ceftazidime-avibactam and how that impacted whether it was possible to enroll in the colistin-compared superiority trial and then secondly you mentioned the emergence of colistin resistance and comments on the rationale for excluding these patients rather than randomizing them to a treatment regimen or best available therapy regimen since that may be the one group where it is possible to evaluate a treatment effect.

DR. FRIEDLAND: So first on this ceftazidime-avibactam, when we started the trial, ceftazidime-avibactam was not approved, was not available and in fact even now most of our patients are being enrolled in Europe, where ceftazidime-avibactam is not yet available. But it does speak to the fact that these kinds of trials do have a limited lifespan because as new therapies do become available,

it does become almost impossible to run a trial now versus colistin, in which we have more effective treatments. So I think this is also part of the problem of these trials, is that you can only run them for so many years before new therapies become available and the comparator you chose is no longer now, you know, a valid comparator.

What happened with colistin is when we started the trials, colistin resistance wasn't as much of a problem as it has become. So clearly investigators were keen to engage in that study with colistin as a comparator. It was one of the few available options. But it sort of became apparent that colistin resistance was a problem and in fact we picked up colistin resistance from our central lab, that the local sites didn't even know about. And we actually pointed out to them that they actually had colistin resistance and then when they started testing more accurately, they realized that they did have a problem.

They do have alternatives, because it is a -- it is a required comparator. It's not a best

available treatment. It's colistin and they do theoretically have other drugs available like tigecycline. So in that situation where they think they have other therapies rather than colistin, they will -- they'd be very reluctant to enroll someone in a trial where they know there's a strong likelihood you can be resistant to the comparator. So in that situation, they'd rather not enroll them in the trial. They'd rather wait to get the colistin susceptibility result. And then, if it's susceptible, they'll run the trial. But if it's resistant, then they're going to look for alternative treatment and not put them in the trial. So I think that's sort of the situation we're in now.

DR. DUDLEY: Yeah. The only thing I'll add to that was actually I think we've chatted with Dr. Alexander, who's running our TANGO II trial. And she actually thinks that it's actually helped, although we don't -- again, Avycaz is not available in Europe yet. But in the United States, it actually has helped the awareness a bit and that patients don't have to necessarily be randomized to colistin. So Avycaz is

fair game in the best available therapy arm.

DR. MARKS: Go ahead, John.

DR. REX: Well, if you listen to the theme there, you know, Avycaz should be increasingly available towards the end of this year. And then, you're going to be filing -- you think you're going to file your NDA when, for --

DR. DUDLEY: Publicly we've said second half -- first half of next year. Okay, so 2017 -- our utility date --

DR. REX: Yeah.

DR. DUDLEY: So 2017. So, and then, plazomicin will come along. So sometime in -- fast-forward two years from now. There could be two or three choices that, you know, are -- each one of them has its quirks. But you know, net of it is it will be really hard to explain to somebody why they should be randomized to colistin. The echo over here was thank God.

DR. MARKS: Sam?

DR. BOZZETTE: Is a general comment in order? Okay. This morning -- okay, never mind. In

general, this morning's discussions didn't hit the role of diagnostics much. And I thought that I should say a couple of words on that. First of all, diagnostics should be able to provide substantial efficiencies in the conduct of these trials by helping to identify who actually has a bacterial infection as opposed to some other condition that put them in the ICU and made them toxic and septic-looking. In terms of rapid identification, and particularly antimicrobial sensitivity testing, probably through genotypes, but they have their issues, the whole genotype/phenotype issue and I think the industry is working hard to get to rapid phenotypic sensitivity. And I suppose in the case of genotypes I should say resistance testing rather than that.

And the other thing I guess I would say is that -- and the thing that really hits me from this morning is the possibility of a virtuous cycle with drug development and diagnostics, the idea that diagnostics could help the conduct of trials, particularly through patient selection up front, by allowing people to discontinue or dis-enroll patients

when it becomes clear that they don't have the organism infection of interest. But at the same time, these trials -- particularly the trials networks are perfect sources for development of diagnostics. One of our big problems is that we don't have a lot of money. And just accumulating the specimen banks is pretty much shoots our development budget for a lot of potential diagnostics.

So the idea that we could draw from both the control and the various active arms in a master protocol context I think is something that would be tremendously helpful for us. And then, the diagnostics that are developed through that mechanism could feed back into the trials, even during the course of the trials. If a trial's ongoing and we develop a better way of determining the patients of interest, that could be incorporated into the trials as it goes along. So I think this idea of a virtuous cycle is something that the group should look at, you know, very seriously. We're going to have some conversations about how to do that and I hope other people who are interested in diagnostics and other

diagnostic companies could participate as well.

DR. MARKS: Any follow-up on that piece? I mean, I think from most everybody I've ever talked to, diagnostics are critical in this as part of the solution. Every report I see that comes out also calls for that as well. John?

DR. REX: Just to extend on that, I really do think that the diagnostics could make trials more efficient. But there's something that Ed has -- it's taken me a while to fully articulate this. The diagnostics enable you to find the patient. But it doesn't make the patient with the rare bacteria more common. So it enables you to find them. It doesn't create them. And so, if the target organism is -- only occurs, you know, 2 percent of the time, it only occurs 2 percent of the time. And the test would enable -- would mean you might miss fewer of them. You'd be able to find a few more. You'd be able to find them a little and maybe the patients you enroll in the trial would be -- once you actually enroll, would be much more likely to have the target organism, the ones you actually enroll. But you still have to

screen the other 98 who didn't have it in order to find the two.

There's no substitute for running the test in a hundred people to get those two. And that's actually one of the things about the trial network concept focused on the UDR setting where everybody with intra-ab gets enrolled is that you could actually inside that be looking for the oddball pathogens because you're actually going to -- you've got something to do for everybody in a UDR-focused study. Everybody with intra-ab in a UDR network gets enrolled and you can run your diagnostic on them and pick out the unusual ones and spin them into something else.

DR. BOZZETTE: I would agree with you that the main utility would be the ability to screen out individuals. You're not going to make more individuals with disease. But if you have -- if you're talking about a condition in which there is an imperative to treat, the difference between only having to do that with a single dose or two doses versus following the person for two or three days should be substantial, I would think.

DR. REX: Right. And the big cost is -- it's the enrolled patient that's the most expensive part.

DR. BOZZETTE: Oh, absolutely. Absolutely.

DR. REX: I say that -- I should really say that -- I don't know the precise percentage. But a big part of our budget isn't just the cost of the patient. It's the running cost of the site. So I've got to have the IDP and the pharmacy. I've got to, you know, go back and audit. I've got to, you know, do all that stuff just to keep the site up and running. And so, that's why the patient cost a hundred thousand dollars. It's not because I spend a hundred thousand dollars on that patient.

DR. MARKS: So why don't we bounce to Nick? Then we'll do Kert and then our colleagues in the audience.

DR. KARTSONIS: I just want to make an additional comment about that and then maybe ask a question to Ian and Mike about their experiences, because we're doing a resistant infection study right now for imipenem-relebactam. And one of the things

that we've done from a diagnostic standpoint is we've -- two years' ahead of time, we actually developed the panels that actually had imipenem, as well as colistin, as well as imipenem-relebactam and literally gave them to all of our sites to use as screening tools, susceptibility panels. That obviously cost time and money to do that. It's not a simple endeavor and I can tell you it cost millions of dollars to implement that.

What it has shown us, and it's probably a poor man's diagnostic, is that, as John has alluded to, we're picking up 1 to 2 percent of all -- and we're obviously in geographically enriched regions that have the resistant infections. But we're still only picking up 1 to 2 percent of all of the KPCs and/or resistant Pseudomonas -- you know, carbapenem-resistant Pseudomonas pathogens and what have you. So I guess a question I have for Mike and Ian is have you used any enrichment tools? Have you used any diagnostics that might help you expand on TANGO II that you're willing to share or from the CARE study?

DR. FRIEDLAND: So we allow our sites to use

whatever rapid diagnostics they have available. And a lot of our sites, like in Greece, do have rapid diagnostics. We don't have one specific diagnostic that we -- you know, that we demand. But a lot of our sites do use their local -- and that has been very helpful. They can enroll patients sooner with that.

DR. DUDLEY: Yeah. My colleague, Jeff Loutit, is actually at the microphone and we have actually discussed this. So maybe, Jeff, if you want to comment on how we have been thinking about enrichment with the diagnostics and so forth?

DR. LOUTIT: Yeah. Thanks, Mike. And this speaks to the comments from John and Sam as well. So as part of -- so I work with Mike as part of The Medicines Company and work with Elizabeth in running the TANGO II trial. We're part of the consortium to develop a cartridge through Cepheid to look at identification of CRE directly from specimens -- so urinary tract or respiratory tract specimens, et cetera.

What was very -- and we then went out and found that pretty much every site that we were going

to, had the GeneXpert system. So we knew they could do it. And then, we said, okay, how about actually screening all these patients who have suspected CRE. And you saw the numbers that Ian put up there, essentially screening close to 600 patients to get to 14. And the microlabs just looked at us and said, you're out of your mind. So we cannot -- we could not get at least the microlabs to want to take on that work to screen patients into the study. So we have the test. We have the patients. We have the machine to run the test. We just don't have the ability for the microlabs to do that.

DR. MARKS: Thanks. Kert?

DR. VIELE: I was going to mention that the notion of trial networks in this context with diagnostics, having a network and having multiple drugs, a lot of the newer platform trials that are being run in, say, oncology, they partition a patient stream on the basis of biomarkers, if you have a HER-2-positive breast cancer, you're eligible for certain drugs in the study and not others. Having a network and a central way to do that kind of screening -- you

know, if you imagine that you're running a trial and he's running a trial and you can't enroll the exact same patients, when you encounter a patient that you can't enroll but he can, having a way to take that full patient stream and just efficiently getting it to the drugs that are still in the running for that patient population would be valuable.

DR. DUDLEY: Yeah. I would agree. I think the interesting question here for Sam -- I'll get there in a second. But the elephant in the room right now though is that what we're hearing is that developing these tests for clinical trials from a diagnostic industry standpoint, okay, maybe. But a diagnostic test for use in clinical use for doing exactly what Jeff just described in clinical practice, not enough of a market there. So maybe you could help us understand if that's -- you know, is that something the way that you see the universe or because I think, yes, having a diagnostic to help us get a clinical trial done is great. But I think what clinicians' expectations are is that they'd really love these direct specimen tests to be able to make those

decisions at the bedside, to be able to put patients on the appropriate drug.

DR. BOZZETTE: Okay. Let me -- let me one quick comment on the microlabs. One of the barriers to rapid diagnostics is the tradition of microbiology. There are expert systems that will release identifications from automatic machines automatically. They are essentially always right. And at least they're as right as a human would be.

But people are reluctant to turn them on because microbiologists are used to looking at the results and releasing the ones that they think are most appropriate. In addition, microlabs tend to run only during the day or at least into the evening. So if you have a diagnostic that takes two or three hours, you run the test at 8 o'clock at night, no one's going to know anyway. And so, we face this when you shorten, say, times to positivity in blood cultures. You know, if a result falls in the forest at 3:00 in the morning and there's no one there, does it make a sound? And the answer is no, it doesn't.

So I think part of the clinical trials

infrastructure should involve buffing up laboratories and increasing laboratory capability. Now, in respect to developing tests, we have two problems. One is that we face commodity pricing. We don't have value-based pricing. When a test comes on, they'll look at the cost of a similar test and say, okay, that's what you get. So we get -- I don't know, we'll get $80 to do -- to run a companion diagnostic test on an oncology drug that's costing $60,000, $80,000 a year. So we face commodity pricing.

And the second thing is cost of development. And so, when you look at the NPV for narrowly focused tests, it's just not there. So why are we willing to develop specific tests for specific trials and specific drugs? Frankly, because you guys are paying for it. And so, it lowers the development cost and our marginal costs, you know, our marginal cost to production will be hopefully not that high and we'll make some money back. So what's the answer? I think what we've heard in terms of decoupling for pharmaceuticals needs to be developed for diagnostics as well. So fixed amount of pharmaceuticals, paid for

in an upfront payment of some sort, market entry fee, whatever. And something similar needs to happen to the diagnostics that would go along with that indication.

Now, in microbiology, the diagnostics are not going to be true companion diagnostics for a lot of the reasons that John has pointed out in terms of the variety of alternatives and stuff. But when you get into tomorrow -- I'm sorry I won't be here -- you may get to the point where we're talking about something that really is a true companion diagnostic. And in that case, we're going to have to tweak the model because the oncology model frankly isn't working for us.

DR. MARKS: We have a colleague over at the microphone over there. Just your name and your affiliation, please.

DR. CONNELLY: Yeah, Lynn Connelly, with Achaogen. So I work with Ian on the CARE study. In addition to rapid diagnostics, we can look at patient characteristics or epidemiological factors that place them at high risk for infection by the target

pathogen. We found that very useful in the context of our study to allow patients to enroll on the basis of being known colonized with CRE or because they reside in an ICU where the rate is so high of CRE. So we can look at things that are less technologically challenging in order to help in all these studies.

DR. MARKS: David, your name and your leisurely retirement affiliation?

DR. SHLAES: Yeah, David Shlaes, retired. So after hearing today's presentations, it kind of brought me around to thinking about tomorrow. And I had a few thoughts and questions I'd like to share. One question is, Ian and Mike, and we just talked about this, but if you had a drug for which there wasn't the non-inferiority possibility -- so pathogen-specific -- given your experience with your CRE development programs and the kinds of patients you have to study, would you as a company be willing to take the risk to do it? And you know, I think that one of the jobs that we'll have to undertake in terms of thinking about feasibility for pathogen-specific drugs, which again I guess we'll talk about tomorrow,

is how do we de-risk these sorts of trials. And I think it'll be -- as we talked about earlier, it'll be important to think about external controls.

The other comment I'd like to make is given the importance of pharmacokinetics and PK/PD in the way we're going to be -- we're thinking about the drugs that we're talking about today and even more the ones we're going to be talking about tomorrow, from kind of a commercial perspective, when you think about how you're going to deal with this with physicians and hospitals treating patients, especially in the United States where 70 percent of hospitals are under a hundred beds or under 200 beds, this is going to require a huge -- I believe a huge educational effort to make people understand that PK/PD can actually contribute to their decision-making process for individual patients. So I think those kind of two things, along with external controls, they all kind of make a set of issues that we still have to grapple with. But I'd be interested in comments, especially from Mike and Ian, on that.

DR. FRIEDLAND: I'll go first on part one.

You know, this is the reason why we're having this workshop and why there's the whole discussion tomorrow is because I think we all recognize that there are therapies in development that are pathogen-specific. And I think without figuring out what are the pathways to get these developed is a major disincentive to continuing those programs. I am hopeful that we will come up with something because pathogens like Acinetobacter is far too much of a problem without us coming up with some sort of solution on how to treat these. But I think you are right in that we do have to have some assurance that there is a pathway before one will actually sort of undertake these clinical trials. We may develop them up to the point we get to Phase I and PK/PD. But without knowing the clinical pathway, it's not going to go much further than that.

DR. DUDLEY: Yeah. I'll just add a couple -- I may keep our powder dry until tomorrow on the single pathogen. But what I will tell you is that, you know, we have intravenous minocycline, which we recently had approved with a new formulation in the United States. And we'll be looking at a program for

Europe where Acinetobacter, as you well know, is, if anything, a bigger problem for multi-drug-resistant Acinetobacter. So that'll -- we'll talk a little bit more about what our thoughts are about that tomorrow and how that might -- how one might go through that, where clearly a non-inferiority trial is probably not going to be very feasible there.

What I would say about the PK/PD question, I think that a lot of us that have been working in this area have recognized that the educational component needs to come with better software and better ways of communicating what the PK/PD is telling us.

So I will -- and Paul may want to comment on this, and I -- because it's his program -- but I think that PK-PD Compass program, which is an iPhone/iPad-based program which I think really takes all of that information and sort of demystifies a lot of the mathematics and a lot of -- uses real-time information either from an individual hospital or from surveillance data, epidemiologic data and using the best available information that we have about clinical pharmacology of these drugs is going to help us I

think make better decisions as it relates to thinking about things as not sensitive or resistant, but thinking about -- I think, as one of our panelists stated here, is that it's a distribution of exposures and a distribution of MICs that will help us make better decisions at the bedside. And I don't know if you want to add anything more, Paul, to that, but -- thank you.

DR. MARKS: Well, we might be interested in Helen's perspective on these in the clinical utility realm of this type of approach.

DR. BOUCHER: You know, I agree a hundred percent and I think that we see stewardship programs as a major vehicle for helping to do this. I mean, we have thankfully a few new drugs and all of those are being used in stewardship programs where they exist an we're really happy that CMS has its proposed rule to make stewardship a condition of participation in hospitals in the U.S. I think the form that stewardship takes is going to be different. You know, to the -- to Dr. Shlaes' comment about the 80-bed community hospital, it may be that a stewardship

program in that setting is like one that one of my former fellows is running now in North Carolina where she sits in Charlotte, but is in charge of stewardship for academic hospitals, community hospitals and indeed physician practices where the largest amount of antibiotic overuse takes place.

So you know, stewardship is not always going to be what we have at Tufts. You know, it's going to be different things. But thankfully, I think the era is coming where we'll have more and where tools like Dr. Ambrose's tool can be used. I would still advocate you need the experts who use it and interpret it and the doctors who we serve largely when we see their patients want what drug at what dose and for how long do I give it.

DR. MARKS: So we'll go to John, and then thanks for being patient, and then we'll come to the audience. Thank you.

DR. REX: So picking up on this PK question and unusual populations and sort of thinking about what I said earlier about, you know, pediatrics, you're often thinking about extrapolating based on

just getting the PK right in the neonate. One of the changes that has occurred for FDA labeling in the recent years has been that the information around pharmacology has been more and more limited to just the approved indications, and for reasons having to do with the way the Code of Federal Regulations talks about what you can put in the label. And I'm not quite sure for EMA where that is.

But I'd like to I guess ask our regulatory colleagues to think out loud about the question of providing the pharmacology data for other scenarios. And in the case of pediatrics, it's little people. And in the case of the rest -- you know, everybody, it's oddball body types or odd physiologic conditions, that sort of thing. So it's this notion -- in a sense, it's analogous to the second group of organisms in the microbiology section where the first group, we talk about the ones that actually have clinical data. The second group, we talk about ones where, well, we've never actually studied it, but it looks like it might be susceptible.

And so, I'm thinking about those themes and

wondering if that's something -- because we've heard a couple of calls for information in the label from these difficult trials. And it feels like sort of the minimum thing you could get at would be in the spirit of the way we did pediatrics and dosing, could we do that here.

DR. COX: All right. So let's see, maybe I'll start out -- I mean, you are right, John. I think it was -- I don't know if we used to do it. But I know -- I mean, even 15 years ago, we -- you know, the attention to the information provided with regards to drug levels, you know, in various different tissues is, you know, one where the labeling would include information for sites that were relevant, you know, to the approved indication.

So if you had a skin indication and you had a blister fluid study, the information would be in there. If you also had, you know, information about ELF levels, but it didn't have any sort of pneumonia indication, then that indication would not go in the label. So I think this stems from sort of a balancing of providing information, you know, that's consistent

with the approved indications and then some concern about providing information that might in essence sort of enable off-label use in the setting of not having an indication that was relevant to the particular tissue fluid level.

You know, this is something that we've been looking at a little bit more over, you know, the last, oh, couple of years, I'd say, you know, because it's coming, you know, more apparent that there are situations where such information, you know, could be helpful to folks. It is information too that is, you know, essentially straight factual, if you will. It doesn't tell you that the drug is going to work. It does provide you some information about the level in a particular tissue fluid. So I would say, you know, this is something that we're still looking at and trying to figure out, you know, how do we balance, you know, providing this information. What's the implications for the approved indications, for indications that are essentially not approved or, quote, unquote, "off-label"?

And then, the other thing too that we always

have to be mindful of is that we generally try and take approaches that, you know, are the same. And so, you know, we think about these things a lot of times from the standpoint of the particular therapeutic areas that we look at in, you know, our groups. But there's also implications too for other areas. So there's you know, a fair degree of, you know, trying to navigate through all of the implications of doing something about including information about tissue sites that might be, you know, related to indications that are not approved. So but yeah, no, I understand. And this is something -- we've talked about it at meetings before over time. This has come up, so --

DR. MARKS: Marco?

MR. CAVALERI: Yeah, I think we are completely in line with what Ed just said about sort of being careful, not promoting off-label use. But of course in the context of the potential of granting an indication per pathogen, it may come up the issue on how to provide information to the prescriber about different set of infections that we did not study, which could be don't do that because the PK is not

supporting you. But it might be that the PK is good enough. So you may consider that. So I think here, in that context only, it would be important to try to reflect about how best we could include this kind of information in the SmPC.

DR. MARKS: Thank you, Marco. So we'll bounce to our audience. Name and affiliation, please?

DR. KINDRICK: Sure. Amy Kindrick, from Genentech Roche. I'd like to go back to something that was touched on briefly earlier today and that is the issue of excluding patients with prior antibiotic exposure. The interval I think is 72 hours within which only one dose could have been given. And I think Mike Dudley or Ian Friedland -- I can't remember which -- pointed out that it's one of the major reasons for screen failures. And it's a bit of a conundrum because one of the things we know for sure is that prior antibiotic exposure is one of the biggest predictors of antibiotic-resistant infections. So it's really an effort to try to balance scientific rigor with the reality, which is that, at least in our experience, large numbers of ICU patients violate that

prior antibiotic exposure. So does the panel have any thoughts about ways that potentially we could address that when we're looking at drug-resistant infections?

DR. COX: So maybe just a few comments on the issue. So -- and Dan and Sumathi are going to correct me if I stray here. But essentially, if you're doing a superiority trial, you can have prior therapy. It doesn't really -- I mean, it decreases your -- it may decrease your chance of showing superiority if it's effective therapy. But in the setting of a superiority trial, you could use prior therapy. Another situation -- but if you use too much of it, you may treat the infection and then the ability to show superiority may essentially evaporate.

There are situations too where patients get prior therapy and essentially they're failures. They're not responding to therapy and you continue to have positive cultures. So in that situation, the presumption is that you're really not affecting the course of treatment. So that patient could still be enrolled. You know, and we describe that in our guidance documents that talk about non-inferiority

trial designs and, you know, I've already said for superiority, you could give antibiotics. So you could obviously do it there too.

Now, the issue becomes if you're actually treating the infection. You know, and we've heard about the importance of those early doses and, you know, the literature bears that out too. The early doses in serious infections are so important and, you know, getting effective therapy on board within hours or less, you know, in order to be able to reduce mortality. You know, and if you've actually had a significant impact on the infection, it can be difficult to, you know, do a good test of the antibacterial drug. And no one wants an antibacterial drug out there that we really don't know if it works when it's being used for patients with serious infections.

So you know, so now, to get to what do we do about this, so the CTTI folks are tackling at least one approach to this. And the way Vance Fowler describes this is that, you know, if there's only so far that we can go with prior therapy on this end of

the equation because we'll be treating the infection, what can we do over here. So the CTTI folks are working on a study in HAP/VAP with the first observational phase to understand, you know, who are the patients who are developing HAP/VAP. Can we identify risk factors? Can we pre-consent patients? You know, are there other mechanistic things that can be put in place to minimize, you know, the need for, the pressure for, you know, longer courses of therapy before getting into a trial.

And I think, you know, those sorts of efforts -- I'm very optimistic about this -- I'm hoping it will help. I'm hoping that it will allow for patients to be, you know, more routinely enrolled into the trial with shorter durations of prior antibacterial therapy. And if you look at our guidance documents, we do allow some prior antibacterial therapy just because if we didn't, it would be probably impossible to run a trial.

And in particular, we think it would be difficult to have sites in the U.S. So we are trying to balance these two issues. And it's a difficult

situation. I think this underscores really, you know, one of the very difficult challenges in studying an antibacterial drug -- the urgent need to start therapy, you know. This can happy anywhere at any point in time to any one patient. You know, and you don't really know exactly what you're treating when you start this first course of therapy out.

So I think there are efforts being made. But it is a tough problem. And you know, it's not just prior therapy too. But we'll be talking more about this too tomorrow. But it's concomitant therapy also. And you know, to get drugs that don't overlap with the spectrum of your investigational drug, particularly at the point in time when you're initiating empiric therapy, can be really difficult.

But at the same time too, you know, if the concomitant therapy is all you really need, then, you know, the quality of the test for assessing the test drug is, you know, really pretty limited. So yeah, so maybe my final comment on this is that I think we all -- you know, we're all trying to do some things to try and make this better. But it is a -- it is a

difficult problem, so --

DR. MARKS: But you certainly don't want to delay starting therapy while you're trying to get informed consent for an investigational agent. So that ability to at least start something makes a big difference. Marco, any other add-ons?

DR. CAVALERI: No. I think I fully agree with Ed. This is a very difficult topic. We are putting efforts in trying to allow as much as possible. But we have to be careful in not contaminating the data. So we are open to discuss evidence that is emerging and whether we can allow more. But at this stage, it's difficult to go beyond what we are recommending.

DR. MARKS: Thanks. And over to the microphone again? Name and affiliation, please? And then we'll come back to you, Aaron.

DR. HILLAN: Ken Hillan, Achaogen. At the recent ASM, I had an opportunity to talk to someone presenting data on Avycaz and I was asking about susceptibility testing and what they had seen. And they said they didn't know because they actually

didn't have susceptibility testing available in the U.S. at their institution. I also went to a seminar at ASM and had an opportunity to learn that it can take three to four years sometime to have broad availability of antimicrobial susceptibility testing. And it seems for these new drugs, we've made amazing progress in getting rapid regulatory pathways to approval.

But some relatively basic things, like broad availability of automated susceptibility testing takes so long. And it seemed, at least if you were trying to organize this a priori, you would want the availability of the testing to be available exactly the same time as the availability of the drug. And I wondered could people comment on what we should be striving for moving forwards and what we can do to streamline the process to make both the drug and the susceptibility testing available at the same time.

DR. COX: Go ahead. You do it.

DR. NAMBIAR: Yeah. So thanks for that comment. I think we're acutely aware of the issue and we've heard it from many different stakeholders, be it

sponsors, drug companies like you or clinicians who are trying to use the drug because I think the point you make is very valid. Having that drug approved just doesn't make it, you know, easy for the clinician to use it and use it appropriately. It was very important that these products be used appropriately in the right patient.

So having said that, we know it's a problem. We've heard this in other fora and we are in close conversations with our colleagues at CDRH and hopefully in the coming few months we plan to have a public discussion. So I think that would be very good, where we can facilitate the process and the interaction between the various stakeholders to be able to find the solution forward. So I think we recognize that this is important and need to address it. Thank you.

Oh, yeah, and Ed reminded me, I think there's also work ongoing -- I don't know if anyone from CDRH is here or not. But there is ongoing work on a draft guidance being published on co-development of diagnostics and that touches upon AST devices as

well with drugs. So that's forthcoming. I don't have an exact timeline. But I think your comment is very timely and we are aware of it and we should hopefully start the conversation soon.

DR. MARKS: Aaron? Oh, David?

DR. SHLAES: I was just going to add --

DR. MARKS: You've got a follow-up?

DR. SHLAES: A lot of this is not really a regulatory problem. It's a diagnostic company issue. So what we used to do in the old days is we would give laboratories discs because the disc criteria are available immediately on approval. And they would use the discs and get an idea of what the susceptibilities were in their hospitals and that was a reasonable interim step. These days it's harder because microlabs are more constrained. But I think it's an important problem. But there may be ways to deal with it.

DR. MARKS: Thanks, David. Aaron?

MR. DANE: Yes. It's kind of a question for Mike actually. But, so Mike, you were talking about the idea of like a CRE network rather than a broader

network. And I just wondered how that would work, you know, because if you had a much narrower population you were going after, is how you would set up the network in terms of where you go and also getting more cross-sponsor commitment to do that when not everybody's going to be going off to CRE, for example. So I didn't know how you saw that. That maybe --

DR. DUDLEY: Yeah. Can I have my first slide -- no. That's a tall -- that's a tall order. What I -- what I guess I would say is that what I believe I've heard here is that there is somewhat of a -- I won't say consensus, but I think a recognition that this type of information is important. And I think that we want to I think take a balanced approach towards looking at this and saying, well, look, there are a number of sponsors that are interested in conducting these types of trials. There are a number of sites and investigators that are interested in developing these trials. We heard from Helen that a lot of them would like to participate, but not having some sort of base support to build infrastructure within their institutions would be helpful.

So this to me sort of sounds like we're asking the right questions when we're asking -- when we're trying to establish trial networks. I think that we would just say that it may be useful for us to think about it in the context, and at least from our perspective, that need is more to try to create the infrastructure to get these sicker patients into the trials and to get the proper GCP training and base support in those laboratories. Look, we're not going to solve -- what we want is a network of engaged clinical investigators that are in infectious diseases.

And that isn't necessarily what happens in a cUTI network. Those are urologists and people are treating patients in the outpatient. So I think if we want to, you know, address this problem head-on with the best minds, I think I would advocate that let's try to figure out how to crack this problem of getting the sicker patients with CRE into a network.

MR. DANE: Yeah, and maybe that's what I was thinking, is you could do both at the same time in some sense.

DR. DUDLEY: Yeah.

MR. DANE: So if we have a network that isn't too narrow, we can -- we'll get some resistant pathogen data. I mean, we talked about the operational efficiencies. The other factor that's incredibly important is it can be a much more efficient use of data and patient data because we can share control on. So we could do all of that and try to address some of these resistant pathogen questions at the same time I think.

DR. DUDLEY: Yeah. I think clinicians would like to know, out of those 69 regimens that we identified in our natural history, which of the few of those look pretty good. And so, I think strategy trials and, you know, Sam mentioned ACTG and I'm from that era as well where the clinical trial networks with AIDS clinical trials was instrumental. And not so much in actually developing new drugs. It did do that, but it actually was understanding strategies of how to use them. Do I start with two drugs or do I start with three drugs? When do I add the third drug? What patient populations benefit by that?

Those were enormously important questions that served as the basis for HIV treatment guidelines for decades and they were based on those. So yes, let's go ahead and create a network now and answer the question what is the best available therapy. So, and then set that framework so that we can start rotating these new therapies in, much like what others have proposed.

MR. DANE: I think the other aspect to that -- we were talking about over lunch, which is if you got to a point where that network and the data were broad enough, you might even be able to have a new product coming through and you can somehow try and match the patients to the appropriate ones that you've got. And that might give you a more meaningful comparison than what we try to do at the moment.

DR. COX: Yeah, maybe just to follow up, and Aaron, you may have been hinting at this, if you've already said it. But I'm trying to figure out -- so if, you know, resistant phenotype is not really a determining factor per se, but it's more patient comorbidities and patient factors, I mean, surely

there must be other patients out there with similar comorbidities, similar factors who don't necessarily have the resistant phenotype. I think that may be what you were getting at.

MR. DANE: Yeah, last point, that's exactly it. Yeah, so it might be that you can try and match people up a bit more and you'll have a richer data set to do that with.

DR. COX: If the particular resistant phenotype is really so rare that it's hard to constitute the trial. But if there's a lot of other similar people with regards to other patient factors but, you know, they may have the organism, they may have -- you know, they may not have the particular resistant phenotype. It seems like that may be the sort of information that could be helpful and then you wouldn't necessarily be so restricted by the prevalence of a phenotype -- resistant phenotype that's exceedingly difficult to identify.

MR. DANE: Yeah, and you're more likely to get that in a network than just your single narrow trial where you may get a couple of patients like

that.

DR. MARKS: Sam?

DR. BOZZETTE: Can I say something about why development diagnostics is low --

DR. LOUIS: Just one more quick promotion of networks and that is for patients who may not be available for any of these trials and are in what would hope to be an observational database, you'd still want to have it be observational and not passive with standardized data collection. And that really won't happen I think without some kind of a network wrapper on the whole thing.

DR. BOZZETTE: I think that to accelerate the development of automated diagnostics, what's going to have to happen is to have -- for these purposes is to have sort of a stable pipeline of customers, meaning pharmaceutical companies. And we need to start collaborating much earlier than we do now. It is not so easy -- it's not the same thing as developing a disc or an e-test where you can just say one drug because there are only a limited number of slots in these cards. And every time we change one,

we have to make an essentially new application because it's a new card. So it's complicated, but doable. And I think that, as I said, what we really need is to upstream the collaboration so that this just works better for everybody.

DR. COX: I might ask -- I mean, we're almost at 2 o'clock. But before we, you know, leave this little section -- and we can come back to it later if there's a whole bunch more thoughts -- but a difficult problem. You know, we've heard some about, you know, the patients that we might see in a non-inferiority trial. We've seen data about who actually gets in to, quote, unquote, the "resistant", you know, pathogen studies that have been out there. Some of the PK differences. We've heard some of the ideas about how we might approach, you know, the PK being one of the things we can measure. You know, Aaron was mentioning the idea of, you know, maybe you can enroll patients with similar comorbidities who didn't necessarily have the resistance phenotype of interest.

I'm wondering are there any more thoughts on potential ways to address, you know, the issue of, you

know, the differences in the patient populations to get at, you know, how you could generalize information beyond these two ideas, both of which are good ideas, because it seems like this is an important issue. Other thoughts or other ways we might tackle that? And if there's nothing, maybe -- you know, we can always come back to it later on if people come up with good solutions because it's a difficult problem. And that's why I'm asking the question. I think, you know, we've got two good ideas about things that could be done. I'm just wondering if folks have any other thoughts.

MR. DANE: Well, I guess if you were confident enough about the characteristics you had or are there other external sources of information you could draw upon. I mean, I can't think of any straightaway. But that might be another potential as a way of providing some context for what you see in some of these smaller studies, particularly in areas where we anticipate the responses to be pretty low. So then you can say, well, if we have got a relatively small number and the responses are much better, that

gives us a lot of confidence about what we're doing.

DR. MARKS: One final question before we go back to the presentation. Name and affiliation, please?

MR. MOORE: Sure. John Moore, unemployed. I have a -- I have a -- regarding the automated susceptibility testing, I understand that by adding one drug, you've got to take another drug off. Has there been discussions around trying to develop a panel, whether it be Vitek or MicroScan, of drugs in which -- are used for unmet medical need. For example, when you run your primary panel, if you get a certain resistant phenotype, a resistance to this, this and this, then run your secondary panel that has all the other drugs on it. That way, you don't have to worry about taking a drug off and adding another one on. Has that been discussed at any length somewhere?

DR. BOZZETTE: Sure.

MR. MOORE: Yes, it has? And is there any -- is there opposition to something --

DR. BOZZETTE: Well, you --

MR. MOORE: I can see how a company would not want their drug to be on a secondary panel. But reality is that's how they're utilized.

DR. BOZZETTE: The real issue is the one at a time thing. You know, so do you make a card that has two drugs, three drugs, you know, when in fact we're looking at, you know, 64 and soon to be a hundred well cards. So you know, the trouble is that the economics of the N + 1 drug is not good. But I agree with you that, you know, secondary cards -- and we do do that actually, secondary cards or cards for specific markets, like Japan where they have a different profile of drugs that are used and that sort of thing is something that we do, and we could do more of, I suppose.

SESSION 3: STATISTICAL CONSIDERATIONS

DR. COX: All right. Well, thanks. We're at the 2 o'clock hour. So I thought we'd move on to our next section to talk about statistical considerations for studying drugs that are being developed for treating patients with unmet medical need. And our first speaker of the session is Dan

Rubin. Dan's a statistician with us here at FDA. And he's worked with us on a number of different antibacterial drug applications and also with some antiviral drugs. And we appreciate Dan's willingness to give the talk with us here today. He's always a source of very interesting ideas, as he not only tries to understand the statistical issues but some of the other practical and, you know, clinical issues faced with studying these drugs. So Dan, the podium is yours.

EVALUATING ANTIBACTERIAL DRUGS IN UNMET NEED SETTINGS

DR. RUBIN: Well, thank you very much for the opportunity to present today. I'll first discuss randomized trials in the resistant pathogen setting, focusing on several examples, the potential for platform trials and trials that combine subjects with infections at different body sites. I'll then discuss challenges and options when it's very difficult to enroll large numbers of subjects with resistant pathogens, including differences between inferential and descriptive statistics and differences between

Bayesian and frequentist statistics.

The table on this slide is showing four recently published randomized clinical trials that compared colistin monotherapy to colistin combination therapy with either rifampicin, fosfomycin or meropenem for treating life-threatening carbapenem Acinetobacter baumannii infections. The fourth trial is still ongoing and Acinetobacter is the dominant, but not exclusive pathogens. And you can see that the trials together have enrolled about 600 total subjects. And they're addressing an important question, because if combination therapy is improving survival, then that's a major benefit. If it's not improving survival, then the benefit-to-risk profile would be unfavorable because rifampicin, for instance, would lead to a lot of drug-drug interactions.

The table on this slide is showing the mortality results in the three completed trials. You can see from the pooled results that we don't actually have an answer yet for whether combination therapy should be given to these patients. There was approximately 50 percent mortality in both subjects

randomized to colistin monotherapy or combination therapy. But the confidence interval for the treatment difference can't rule out a mortality benefit from combination therapy of as high as 15 percent.

Now, fully powered randomized trials would provide the most statistically reliable answers to the most important questions, such as this question with combination therapy. For complicated patients with many comorbidities, randomization ensures that treatment effect estimation is not confounded by baseline differences between treatment and control groups.

The most natural questions in this setting are superiority questions because patients with effective therapeutic options could be folded into more traditional non-inferiority trials. However, as shown in the previous example, to obtain definitive answers, it must be possible to enroll a relatively large number of subjects with infections due to multi-drug-resistant pathogens. So discussion topics for today have been what other strategies are there to

increase enrollment and then what can be done if it simply is not possible to enroll large numbers of subjects.

One method to make trials in this setting more achievable, as we've discussed today, are platform trials and a platform trial using a common master protocol could potentially allow for a study of multiple antibacterial drugs, studies of multiple indications or a study using a shared control group. Just from sharing a control group, the potential gains are if two sponsors run separate trials of drug A versus control and drug B versus control with 100 subjects per arm, the sponsors together must enroll a total of 400 subjects and compete for study sites. But if instead there's a three-arm trial with drug A, drug B and control with 100 subjects per arm, the trial only enrolls a total of 300 subjects rather than 400 subjects. And separate statistical comparisons could be made for drug A versus control and drug B versus control.

In a straightforward platform trial design, drugs would enter/exit the study in a staggered

manner. The study would attempt to answer multiple questions of interest. There would be advantages in shared clinical trial infrastructure, study sites and IRBs. The study would be able to prospectively plan for how comparisons would change if the standard of care regimen had to be updated due to ongoing trial results. And the comparisons of interest would be between subjects concurrently randomized to tested control drugs.

The slide here is showing the abstract from a prostate cancer MAMS trial, standing for multi-arm/multi-stage trial, which along these lines was a seamless Phase II/III design that uses shared continuously updated control group to evaluate multiple interventions for prostate cancer. It's important to note that many statistical design features could potentially be part of a platform trial, but are separate issues that would need to be considered independently of whether to evaluate antibacterial drugs using a common protocol. Such issues include response-adaptive randomization, Bayesian adaptations for efficacy and futility,

stopping criteria or use of statistical modeling with non-randomized comparisons such as comparisons between subjects in the trial assigned to drug A or drug B who are not concurrently randomized.

Now, beyond platform trials, another method that may make studies in this setting more achievable would be to combine subjects with infections at different body sites. To illustrate the potential utility, the CDC says about carbapenem-resistant Enterobacteriaceae that patients whose care requires devices like ventilators, urinary catheters or intravenous catheters and patients who are taking long courses of certain antibiotics are most at risk for CRE infections. And some CRE bacteria have become resistant to most available antibiotics.

So then, the question becomes should one conduct a single trial, combining subjects with, say, nosocomial pneumonia, bloodstream infections and complicated urinary tract infections, despite possible differences in endpoints, comparators, durations and patient characteristics and recent examples of Antibacterials that may have had discordant efficacy

results across body sites.

In principle, we can use body site-specific endpoints or responder indices, comparators and treatment durations. And statistical methods can use smoothing or shrinkage to form more accurate body site-specific estimates of treatment effects by borrowing information across subgroups. However, whether to do this is not only a statistical heterogeneity issue, but also a clinical heterogeneity issue regarding whether patients with infections at different body sites constitute a reasonable combined target population because we may have very low statistical power to detect differences in treatment effects between different body sites. And with small sample sizes, statistical methods also can't guarantee accurate estimation for every body site subgroup in terms of having both low bias and low variance.

The table on this slide is showing the percentages of subjects with different body site infections from the three completed Acinetobacter trials that I mentioned earlier. You can see from the first column that pneumonia was the predominant

infection. In one of the trials, about a fifth of the subjects had bacteremia and there was a scattering of other types of infections, like intra-abdominal infections and urinary tract infections. So these were in some cases multiple body site trials.

For the remainder of the presentation, I'll discuss statistical considerations when it's simply very difficult or not possible to enroll a large number of subjects with resistant pathogens in a clinical trial. The sample size table in this slide is showing that to statistically demonstrate superiority with a reasonable number of subjects or even with a few hundred subjects per arm with the resistance marker, the new antibacterial drug would need to provide relatively large benefits compared to current standards of care.

Now, given the sample size calculations from the previous slide, a natural question is whether it's possible to move from studies that use inferential statistics to studies that use descriptive statistics. FDA has traditionally interpreted trials that use inferential statistics and formal tested hypotheses as

providing reliable evidence. Descriptive analysis of a clinical trial would present success rates for drug A and drug B, but would not necessarily formally test a hypothesis. And descriptive analysis is useful for assessing patterns and examples of descriptive statistical analyses of antibacterial drugs include many Phase II studies, pediatric studies and safety studies, including the Phase II studies factoring into the FDA approval of ceftazidime-avibactam in 2015 and also FDA approvals of antibacterial drugs in earlier decades in clinical data used to set susceptibility breakpoints.

So then, a really important question becomes can trials pre-specify decision criteria somewhere between P less than 05 at each body site and post hoc descriptive analysis that would give reasonable operating characteristics in the unmet need setting.

I'll next discuss differences between frequentist inferential statistics and Bayesian inferential statistics. Frequentist methods such as P values and confidence intervals have been the default paradigm for clinical trials. By a type 1 error rate

control, the usual statistical significance level, we mean that approximately only one out of every 40 clinical trials have ineffective treatments, will falsely conclude efficacy. And we have the coverage guarantee that in approximately 95 out of every 100 clinical trials, the confidence interval for the treatment effect will contain the true effect. The nice thing about these methods is that statistical theory provides type 1 error rate control and coverage guarantees under essentially minimal conditions without need for a lot of modeling assumptions or data external to the clinical trial of interest.

Now, Bayesian methods are a different class of statistical methods from frequentist methods and I won't be able in this talk to go through the machinery of how the Bayesian analysis would work or some of the more conceptual differences, other than to say that in practice, this isn't necessarily how the difference between the two types of methods are defined, but in practice, the main difference between using Bayesian methods and using frequentist methods is in how the Bayesian methods attempt to integrate the data from

the trial itself with data or evidence from other sources.

For antibacterial drugs, the prior evidence may come from previous randomized or observational studies of the new drug, comparator or related drugs, previous studies at different body sites of infection, PK/PD data, animal data, in vitro data or expert elicitation. And an advantage of Bayesian methods is that they can attempt to incorporate more of this information into the analysis and formalize for different sources of uncertainty. A disadvantage is that this can lead to erroneous answers if the prior beliefs are incorrect and are debatable or too strongly held. And I'll give examples of Bayesian and frequentist methods in the next few slides.

So we saw earlier in the Acinetobacter studies that in the pooled randomized trials, there were mortality rates of 51 percent for subjects treated with colistin monotherapy and 47 percent for subjects treated with combination therapy. If you pool the studies -- and this is just illustrative, not necessarily to endorse raw pooling as the way that

these studies should be meta-analyzed -- but if you pool the studies, you would estimate a difference in mortality rates to be 4 percent, with a confidence interval from -6 percent to 15 percent. And because the lower confidence limit does not exceed zero and because the upper confidence limit can't rule out a mortality benefit of as high as 15 percent, the usual interpretation is that this confidence interval is too wide to tell us whether combination therapy improves survival.

With the same data, the Bayesian analysis can actually depend on prior information. If we use a so-called uninformative prior that attempts to handle the treatment and control as neutrally as possible, which would imply that before the trial we thought that there was a 50/50 chance that monotherapy or combination therapy had better survival, then the frequentist and Bayesian decisions would tend to be very similar after the trial results came in. however, if we used an informative prior, say that before the trials we model from the available evidence that there's an 80 percent chance that the mortality

rate for subjects treated with colistin monotherapy is between 0.6 and 0.7, then after the trials, we would find from a beta binomial model that there's a 99 percent chance that colistin combination therapy actually improves survival.

So the next few slides illustrate this. The top histogram in this slide is showing the uninformative prior for the chance of death with colistin monotherapy before the trial results. And you can see that it's essentially placing any mortality rate between zero and one for the monotherapy group on equal footing. If you use this uninformative prior, then after the trial results, you'll get the histogram on the bottom of this slide, which is called a posterior distribution. And you can see that the chance of death with colistin monotherapy is centered around the 50 percent rate that was actually observed in the trial.

Conversely, the top histogram in this slide is showing a very informative prior for the chance of death with colistin monotherapy, and which we have modeled based on whatever evidence is available before

the trial results that the chance of death with colistin monotherapy is fairly concentrated at around about 65 percent. In this case, because the Bayesian analysis would depend both on the trial results where we saw a 50 percent mortality rate for this group and the prior evidence, the result of the analysis would be to say after the trial results that there's still a fairly high chance that subjects treated with colistin monotherapy would have a death rate exceeding 50 percent.

In summary, there are opportunities for conducting randomized trials in the resistant pathogen setting using platform trials. A trial combining subjects with different body site infections can be statistically analyzed. But then, the important question becomes how should heterogeneity be addressed. Conducting powered superiority trials in the unmet need setting requires either a large treatment effect or a large sample size. So the important question here is what pre-specified decision criteria are reasonable beyond descriptive analysis. And Bayesian and frequentist methods are both valid

statistical tools. But in the anti-infective setting, the most important consideration is how much weight to give modeling of nonrandomized evidence. And here are my references. So, I thank you.

[Applause.]

DR. MARKS: Thank you, Dan. And building on this construct in terms of innovative trial designs, Kert Viele, director and senior statistical scientist at Berry Consultants, is going to share his thoughts as well. Thank you, Kert.

INNOVATIVE TRIAL DESIGNS

DR. VIELE: There we go. So thank you for having me. The work presented here is funded by ARLG. It's a project directed by Roger Lewis and Brad Spellberg. This discussion has involved a lot of academics, pharmaceutical companies, the FDA, BARDA have been involved in this. One of my goals is really to talk about several different innovations that have all been talked about today, but provide a few more numbers on what kind of savings might actually be encountered.

So we're talking about a trial -- I'm going

to focus on the resistant pathogens. But this is particularly relevant to a network that might enroll UDR and resistant pathogens within the context of the trial. Of course, lots has been said today. It's hard to do inferences on resistant pathogens. So I'm going to be talking a lot on how far can you get in order to bridge this divide between the sample sizes are too small versus we'd really like formal kinds of statistical methods.

Standard trials, we see a lot of trials that focus on one drug versus one control at one body site. And this gets repeated. Lots of trials happen. We've enrolled the control arm in multiple studies. We've got UTI in this study. We've got intra-abdominal in that study. What do we do? So I'm going to talk about three innovations: platform trials -- and all of this is building off of what Dan talked about -- early stopping and sharing information across the body sites. Each of these has the potential to decrease the required sample sizes for trials.

I'll start with platforms. This has been mentioned a lot. It's been mentioned in the sense of

trial networks. But this could also be used simply for three companies getting together and putting their drugs all in one trial at the same time. So this is a scalable enterprise. Some examples, platform trials are being used in lots of areas. One of the oldest running platform trials is something called I-SPY 2, which is a breast cancer study.

Nice things about I-SPY, you can see lots of articles -- not the most recent, but a recent New England Journal of Medicine had four articles on I-SPY 2. I-SPY 2 is interesting from the standpoint of it tries to match drugs to particular patient populations, which may be relevant for resistant versus UDR kinds of mechanisms. There's different types of allocation for HER2-positive breast cancer. Drugs can graduate with certain signatures. We think this drug works in people with triple-negative breast cancer. That's one of the outcomes of that study which may be relevant for antibiotics.

Other examples, so again, just trying to emphasize this isn't new and radical. This is happening in a lot of places. The IMI EPAD initiative

is an Alzheimer's study that's intended to test combinations. If you have a trial network, you have a patient stream that's big enough that you can start thinking about combining drugs in different ways. There's a PREPARE initiative in Europe which is intended to be ready for epidemics. The influenza study of that I think is what Mike Dudley was talking about in terms of a learning health system.

We know lots of things that we think will work. But physicians differ. They make decisions on what they've seen before. The notion of using this health system and having all the data come in. Patients are randomized and in real-time having access to these are the things that are working and these are the things that aren't -- that's the kind of thing that you can do within a trial network and it is an example of a platform trial. GBM AGILE, this is getting a lot of press. If you want to see some really slick videos on YouTube, whoever their PR person is, they're really good. There's also an Ebola trial which, as an example of trying to put together a platform trial that works incredibly quickly of

getting drugs in combinations to patients as quickly as possible. So this is something that we're getting a lot of experience about in the broader realm.

The sharing of control information is the key place that we gain efficiency in these kind of trials. I've talked about 40 drugs here, the notion of doing this for 10, 12 years. But the efficiency gains on the order of 25, 30 percent, even three or four companies getting together, just the mere fact that you've saved a control arm is worth that kind of advantages. So you could really do some good things here.

There are some synergies in a platform. I haven't even talked about early stopping yet. But if you have a platform trial where drugs can go in and out and stop, when one drug stops, another one can come in. Being able to do that, it doesn't work quite like compound interest. You know, you don't double every month or whatever. But this notion of investing savings forward certainly does exist and it's very valuable to combine early stopping with a platform kind of idea.

Platforms in general, if you can run lots of drugs at the same time, savings can be 35 percent. This is a paper that -- the clinical trials paper that's coming out. It may be in print now, but it will be shortly if not. This shows savings up to 50 percent just from the ability of sharing a control arm and being able to stop drugs. I think this paper has response-adaptive randomization in addition to try to tailor drugs to particular patient groups. Early stopping of body sites. We're talking about a trial that enrolls in multiple body sites.

If you have a drug like daptomycin and you're able to see this is failing in HAP/VAP, you can stop that and enroll the HAP/VAP patients in other things. I'm not going to spend a lot of time on this. This early stopping I think is more well understood. But the sample size savings there can often be 15 to 20 percent compared to running a standard trial. One thing to keep in mind, when we talk about formal inferential statistics, if you're trying to get 80 or 90 percent power, you're designing a study with the intent that even if I get unlucky, I still win. That

50 percent power is aimed at if I get exactly what I'm expecting.

To get 80 or 90 percent power, you're saying even if I get unlucky and I get less than what I'm expecting, I still want to get conclusive evidence. If you're talking about a platform and you're going to have 30 or 40 drugs, you're not going to get unlucky all the time. If you're one company, you don't want your one product to die on the vine or one of your key products to die on the vine. But if we're running, you know, 20, 30, 40 drugs over the course of many years, we're lucky half the time. We're unlucky have the time. We may as well make sure we get the savings. We don't need to protect ourselves against -- we don't need to buy an insurance policy for every single drug and early stopping lets us do that.

As I said, early stopping has synergies with platform trials. If you're talking about getting 40 drugs over the course of a decade or more, saving 20 percent, you can evaluate 48 drugs. So again, this notion of paying forward. And I've tried to save time for this one thing that hasn't been talked about much

today which is sharing information across body sites. In a lot of cases, trials are run in, say, UTI or run in intra-abdominal and maybe you're not -- you don't want to run a trial in HAP/VAP because of the expense. The ability to run potentially smaller trials across multiple body sites and sharing the information across those body sites -- excuse me -- has a lot of value in terms of you can get more statistical efficiency and of course it also allows us to see exactly how a drug does perform in those settings rather than having to rely on extrapolation.

I'm not going to get into the details of the modeling here, for the same reasons Dan didn't. It's difficult within the time allotment. But a notion of the kind of fear that you have in running small trials in several body sites. Suppose we ran a trial and we had HAP/VAP, UTI and intra-abdominal together in the trial. And I'm focused on just these are the resistance that come out of this.

So you can imagine a larger trial. I may have several hundred usually. I'm trying to answer the question what about the resistant populations

here. So in HAP/VAP, my control data -- I got 5 out of 12 successes, 42 percent. In the treatment, I'm doing great, 10 out of 13, huge advantage. The problem is if I'm looking for a P value of 0.025, I am a Bayesian, but -- so I've termed this in terms of posterior probabilities and 97.2 percent chance of the treatment is better. That corresponds to about a 0.028. I just missed. Yuck. Now, I'm going to have to go in and ask for, well, was I close enough.

But I didn't just run the HAP/VAP study. I've got the UTI data next to it. I've got 9 out of 25, 36 percent on control, 23 out of 25, 92 percent on treatment. This is fantastic results. This is a slam dunk win. No one's going to question the UTI results here. And then, in intra-abdominal, remember one thing that happens in intra-abdominal, a lot of times you get successes on the basis of surgery. So the control rates are often higher. So I got 14 out of 22, 64 percent for the control and 87 out of the treatment. That's a Bayesian probability of 94.5 percent. It's a P value of 0.055. I missed again. This is not unusual at all in underpowered trials.

When we talk about the notion of I can't achieve statistical, formal inferential statistics in small trials, I'm not saying I can't get trends. I'm saying I can't get 80 or 90 percent power. And this is the type of setting that you're in. This is where you're missing, lots of trials that give you indications, but they're not conclusive.

A key point here though is that none of these data -- while only the UTI is convincing in and of itself, the context here is very important. I just missed in HAP/VAP and I have a promising trend in intra-abdominal. I may not be willing to say for intra-abdominal this is conclusive evidence. But doesn't it matter that it's paired with the other things that are going on? Seeing the intra-abdominal results in a vacuum, this is my only study is one thing. Seeing the intra-abdominal results combined with the fact this is a slam dunk win in UTI, combined with the fact that the HAP/VAP data is strong, this is more evidence in favor.

What the more -- the methods that Dan was talking about for borrowing information across sites,

what they aim to do is essentially partition the variation that you're seeing in the data. They're partitioning it into what kind -- what's the true differences between the sites and what's just result of noise, sampling variability. Here, what we're seeing is general effects. So the differences that we see among these drugs, it's more likely to be sampling variability. These are small trials. We just couldn't recruit enough patients. But the overall trend is consistent. We attribute the variation here to sampling variability and that the true differences are small.

When we fit these models, generally what happens is the effective sample size is increased through this analysis. And good models do this dynamically. So this isn't a situation -- I'm not pooling the data together. Pooling's a very dangerous thing. There's been -- Sumathi was talking about the dangers inherent in this. You never want to put together unlike things. Good models do this dynamically these days whereas if they see common trends, they borrow information between the groups.

But if they see very disparate trends, they borrow a lot less. And that's a protection against the kind of dangers that you'd see when you pool data together.

Back to our sample data set, if you see the bottom numbers in red, what's happened is because these data don't appear in a vacuum, we see each of them combined with strong results. The HAP/VAP data that just missed at 97.2 goes up to 99.7. The UTI is still a slam dunk. The intra-abdominal also went up. The consistent picture has allowed us to increase the effective sample size in each group. And I think this is intuitively what clinicians would do. I know this drug works in UTI. I've got data that says it works reasonably well in others.

What are you going to do? If you can't enroll the big study, you're going to basically do the intuitive conclusion here, which is this probably works. That's what this is trying to formalize and trying to put some statistical teeth on it and statistical teeth in a way that allows us to test the operating characteristics. We can go to the FDA and say here is our design in advance. Here are the error

rates attached to it. This isn't ad hoc, oh, we know we missed, but can't you just give us the benefit of the doubt. This is a way where we know what the error rates are for this procedure.

Here is another data set. This is a situation where intra-abdominal appears to have a significant problem. You can see again HAP/VAP, the treatment is doing better than the control data. UTI, again, the treatment's doing much better than the control better. We actually seem to be doing harm to the intra-abdominal subjects. So they're going the wrong way and I picked this to be an extreme example for a number of reasons. One reason I picked this is to illustrate the dangers of pooling. If you said in advance, I was going to pool the data, what in effect you would do is the good HAP/VAP and UTI sites and the very bad intra-abdominal, you'd pool those together and you'd end up saying my essential conclusion is that nothing is going on, which isn't what the data seem to be telling you at all. It tells you something horrible is going on in intra-abdominal.

This is also intended to be a data set that

shows you the dynamic part of these kind of models. The probability the treatment is better, you can see if I analyze the intra-abdominal separately, that probability is 1.4 percent. That's very low. So again, separate analyses recognize there's a problem. If you do -- if you did pooling, you would pull that up dramatically. You would say, well, I'm just going to average out the HAP/VAP and UTI and you'd say, well, maybe it works in intra-abdominal.

Here, what happens is the model recognizes that the difference between HAP/VAP and UTI, it's more than can be accounted for by sampling and variability and it doesn't pull up the intra-abdominal. So I think there's a lot of hope here to be able to get data in multiple body sites and be able to still make inferences potentially with smaller sample sizes than doing one body site and having a big study and effectively having zero in other sites.

Sharing information, this can save sample sizes 30 to 45 percent. It's substantial. So to give a notion about this is more aimed at a trial network kind of arrangement, but a standard design -- say

you're doing a UTI trial, non-inferiority. You're going to add these features, potentially look at resistant pathogens. A standard design may require 400 to 425 per arm. If you borrow -- and that's across sites, 400, 425 across all three sites.

Borrowing alone can reduce those sample sizes to 300 per arm. If you add early stopping to that, you can get to 230, 275 per arm. There are assumptions attached on this. I haven't gone through all of them. So these are scalable kinds of savings. And then, finally, putting those kinds of drugs in a platform and sharing the control information, it becomes more relevant to talk about this as a per drug kind of issue because you'll have a shared control arm. But that gets down to something like 325 per drug, which is not arms. So these are substantial kinds of savings. And it depends on the assumptions and the treatment effects. But there's a lot of potential here that we can start making more efficient designs and trying to expedite this process.

So in summary, I talked about platform trials, early stopping sharing of information. Main

thing I want to emphasize is there's just a lot of synergies here, the ability to put drugs together. You can start playing with a lot of interesting levers to try to make things work more efficiently. And certainly I again want to emphasize these aren't novel or crazy ideas. These are things that are being done in a variety of areas and hope we can do them in antibiotics. Thank you.

[Applause.]

CLARIFYING QUESTIONS (PANELISTS AND AUDIENCE)

DR. COX: Thanks to both Kert and Dan for your excellent presentations. I just sort of wanted to open it up now for questions about the presentations. Aaron?

MR. DANE: Yeah. I suppose my first comment would be, you know, with Bayesian methods, all the information borrowing, the critical element is the assumptions and an explicit discussion of the assumptions going in. So these are approaches that are quite reasonable. But you need to be able to assume, for example, that the responses are going to

perform similarly across body sites because although it does deal with that to some degree, as Kert showed, you know, you do increase your chance of making the wrong decision, if that's not true. But it feels that should be just a discussion we have up front and decide whether it's a reasonable thing to do and not a reason not to do it. So it's just to state that really, that that's one of the key things here. There's probably additional assumptions that we make when we do this that we just have to be mindful of.

DR. COX: Ian?

DR. FRIEDLAND: I have a comment and then I have a question. So the examples that were given of the platform-type protocols, there are actually -- well, I know at least one example in the antibacterial space. Sivextro and Cubist got together and with the FDA came up with a joint protocol for osteomyelitis in pediatrics. They had a common protocol with a shared control group. Unfortunately, that study wasn't conducted for reasons other than the study itself. It was a financial disagreement.

But I think there are those kinds of

examples. I think pediatrics definitely lends itself to that kind of opportunity. And one would imagine in even in the unmet need space, if two drug developers had drugs for the same target, that there could be a potential for coming up with a common protocol with a shared control group. I just think we don't always think about this in industry that much. That was the comment.

And the question I had is -- and as I said, the statisticians on the panel -- what they think about the DOOR and RADAR analyses that Scott Evans described because those kind of analyses do send to lend themselves to smaller studies.

DR. RUBIN: Yes. I can comment on that since I was a co-author on one of the RADAR papers. So the idea behind here is to use sort of an ordinal outcome, meaning that instead of someone being a success/failure, you have to be able to rank patients. So if you have two patients, you have to say which one of them had the better outcome in terms of maybe, you know, efficacy, safety or some combination. They're actually used in stewardship trials, where if there's

a tie, the patient who's on antibiotics for the least length of time is the winner. And then, what you do is average all of the subjects and try to determine whether subjects randomized to one arm or the other would, on average, have the higher ranking or be the winner. It's been used in some stewardship trials.

So I think it is an innovation that has some utility. It's mainly for superiority analyses. So you'd have to have some type of benefit over what you're trying to compare against. It may not necessarily have to be in terms of an efficacy benefit. It could be a safety benefit that RADAR would also try to take into account.

Now, it's not a -- there's no free lunch here. There are disadvantages of it that have to be worked through. Like any composite, it can be driven by its weakest link, in that a major -- a negative treatment effect on one component of the composite can be outweighed by a positive effect on less components in the stewardship trials if there's a danger that you could approve a less effective drug using this method if it just simply leads to -- the intervention leads

to less antibiotic use. So that has to be taken into account, that it is a different method of given some kind of introduction to it that could potentially be applied in some of these settings.

MR. DANE: Yeah, and I would -- so it's clearly helpful in that compared to our traditional response yes and no, it gives you more granularity than that. So it can give you a bit more information. I guess the challenge often in designing the studies, that you get into some quite complicated assumptions you have to make around if you have five different groupings, for example, you know, if you're moving from efficacy with no toxicity, efficacy with toxicity and then you often end up with five categories.

You've got to make assumptions on how many patients are in each of those different groups to be able to figure out how many patents you need to demonstrate superiority. So that can be a challenge in terms of investing in that study and knowing how likely you are to succeed. And I guess something else Dan just touched on is that the way that works is you're assuming each of those different categories has

equal weight as well. So you're assuming it's equally as important as you go through each of those. So I can see some use.

But at the moment, it feels like it would be a useful tool as a sensitivity or additional information rather than the method you would use to interpret a study because the other thing that I forgot to mention was that you end up with a figure and some evidence of effect. But you don't know quite how to interpret it because it's a number you don't really know what it means. So you'd still have to use it with some of your more traditional methods I think and it just may give you a view of the evidence.

DR. COX: John?

DR. REX: First, thanks for those two really good presentations. And I'd like to ask Dan a question to test my understanding and then that may lead to a comment. So are Dan's slides something that can be brought back up? Because my question will make more sense. Can you go to slide 18? All right. So in this slide, there was a slide before -- actually, back up one, slide 17.

So you analyzed the same data twice, right? And so, the first time you look at it, you say, okay, 51 percent versus 47 percent. So a difference of 4 percent, broad confidence interval. Those look like they could be about the same, or can't tell. It's kind of wide, wide? Next slide. Now, you look at it again and the first time you look at it, you say, I don't know -- the 0.5, the prior 0.5 means I have no opinion. That's the way I should put that into English, is I have no opinion. And so, when I get those data back, I don't know. I'm not much smarter one way or another.

The second time, you say, I have an opinion and I believe that the combination is better. I believe that pretty strongly. So now, when you do the math, would it be correct to say that you've concluded that the combination is better, largely because you believed it before you went in, and the only thing that would have turned you back would have been really a grossly negative result. So as long as it was sort of consistent with your belief, you're happy and you declare victory. Am I saying it correctly in English?

DR. RUBIN: I think you are saying it correctly, that with a Bayesian analysis, if you have an extremely strong prior for what's going to happen, you're going to stay with that opinion unless there's really a lot of evidence to move you in the other direction. This is meant to be illustrative of that. It's probably a stronger prior than anyone would use in a practical analysis with this type of data.

DR. REX: Because I've always wanted to be a Bayesian and yet you've made me not so happy with what that did there because it actually sort of twisted that.

MR. DANE: But John, slide 19, the next slide is actually quite useful for your question.

DR. REX: Well, okay. But I wanted to ask why is this -- but so now my question then spins off of Kert's presentation where, in effect, he showed us data in here little experiments -- intra-ab, UTI and nosocomial pneumonia -- and said, look, you know, they're all kind of the same, you know. Actually, both -- all three of them look like something better than a sharp stick in the eye was happening. So why

shouldn't we buy into that? And he did that without showing us any more math than that other than, you know, these three numbers are all pointing in the same direction. And I'm just -- it feels to me like something about writing these numbers down made me less happy with it, yet I looked at his three examples and I thought, well, that looks not too bad if I just eyeball it. That's not much of a question. I'm sorry. I'm just kind of bothered by what's going on.

DR. RUBIN: That's okay. Well, there were a lot of intricacies in exactly what to model, what the prior is and how the different sources of evidence are combined. And I think that the two examples from mine and Kert are illustrating that, you know, those assumptions and the specific statistical analyses can really change the results. But there are a few other people more familiar with Bayesian methods than me in the room. So --

DR. COX: So why don't we go -- we'll go to Kert, if you're set, Dan. Okay. We'll go to Kert. Then we'll go to Thomas. And then, we'll come over to Mike. Sure. Tom, you willing to take him up on that?

DR. LOUIS: I'll start by saying I'm known as a Bayesian, but what I really am is a statistician who uses the Bayesian strategy for most things, as a kind of guide to navigation. And I think Dan's example -- I'm just going to respond to one or two things and leave the rest for later in the afternoon. But I think whether you're a frequentist or a Bayesian, the only place that beliefs have a role -- and they really have a role in whether you're a frequentist or a Bayesian -- is, for example, in what data are relevant to the current study, whether it be for designing or analyzing.

In Dan's example, if he had used the word that investigators had the belief that the following five studies were relevant to the current study and used those to develop a prior and it was the prior that he put down, there's still belief floating around. But really, the prior subject to at least which studies are relevant is an empirically based thing. And I think in the realm of public policy, clinical policy, put whatever word you want with policy as the last word, that has to be what's going

on in the Bayesian formulism and that we have to always understand the objective properties. And Berry Associates learned a lot of CPU, a lot of this CPU and a lot of that CPU understanding the objective properties of a protocol-driven analysis that is embedded in Bayesian formulism.

And so, I want to push for there being a little less separation of maybe 40 years ago when I would sit around and say, you know, frequentists are idiots -- I no longer say that. I'm sort of a frequentist. The world has gone beyond that, at least for most people, and that we're trying to design and analyze studies doing a good job and that the Bayesian stuff, now with computing available, is not a panacea. In fact, the obligations are greater. But there's no free lunch. But there are a lot of reduced price lunches and we should be going for them. I'll save other comments until later.

DR. COX: Kert, do you want to add?

DR. VIELE: I was hoping you'd say that and figured you'd say it better than me. So I let you go ahead and go. So to piggyback off of that, when we

design trials, one thing that we spend a lot of time on is going through individual data sets and the conclusions that would be drawn from them. This particular example I think is a good one. I think Dan was saying it's a fairly extreme assumption. And it's interesting to see this data set. I think this is almost a treasure trove example. We're making an assumption, 80 percent chance that the mortality rate for colistin monotherapy is between 60 and 70 percent.

That's a strong assumption in there. If it's true, this is the right conclusion to draw from this and that's what the Bayesian machinery is doing. If you're uncomfortable with this -- and I sense that you are -- I think what you're aiming at is not the methodology itself, but that you don't buy the 80 percent chance is between 0.6 and 0.7. And when we design trials, I think that's one thing we like to show to people. Here are the conclusions that it would draw if this data set doesn't make you uncomfortable and basically tease out what are the comfortable assumptions. And the assumption that you may be willing to make here is that not this one, so I

don't want to draw that.

Related to this -- I'm going to talk for a little while, I guess. I might be more inclined in this example. If you look at the -- you've got 88 out of 174 for colistin. There are multiple ways to incorporate the prior. A lot of methods these days include what I'm going to call an off-ramp. It essentially says we've got control data in my current study and I've got this control data from the past that was the basis of this 80 percent belief. A lot of methods these days -- and I think Dan did a simplified example to illustrate things, so not picking on your example at all.

Having that kind of off-ramp I think would do a better analysis here because it would let you see the 88 out of 174. The data that you have in front of you isn't consistent with the assumption. So maybe I should borrow from it less and that would weaken this conclusion that you have now. So this notion of continually having models that check their own assumptions I think are viable and that's what this notion of dynamic borrowing, being able to decide

based on data is it valuable or not is big. And as a final point to this, I think it shows a dichotomy here.

We've talked about historical controls in the past. There's two notions of historical or external controls. There's fully external controls, where there's no controls in the study whatsoever and then there is running a 3:1, 2:1, 4:1 study where you enroll some controls in. And those are night and day. They tend to be lumped under historical controls when we talk about them. But the ability to see control data here is so valuable in testing those assumptions that having some in, I'd always recommend that we have some control data in any of the especially later phase studies that we do.

DR. COX: Thanks, Kert. And Mike still? Yeah?

DR. DUDLEY: Yeah. I think so. Thank you to both of you actually for both the presentations. So let me try this because I think, Dan, you brought this out about the Bayesian priors can come from a variety of different sources. So if we think about

earlier this morning, Dr. Ambrose's presentation taught us that a lot of things that we call failure are just simply because we're too low on the dose-response curve and we've become pretty good about modeling and attaining high probabilities of getting what we consider to be therapeutic exposures.

How would you use that type of information then to come up with a prior that would help you then to sort of become more confident in your small trial observation? So in other words, if we carried into that trial a prior belief that a dosage regimen is going to provide a certain level of exposure that's going to be attaining a pre-specified target, would we be able to use that to sort of strengthen our conclusion, sort of, to use Kert's term, borrow from that to help us understand?

DR. RUBIN: Right. That's a great question. And at this point, you've kind of put me on the spot. But I don't think FDA can necessarily endorse or not endorse that type of analysis. In the past, that type of data has been more hypothesis generating data, used for dose selection and used to set up candidate drugs

to see if they'll work really in the full standalone test of a Phase III trial. In terms of using an analysis that formalizes the borrowing PK/PD data and integrates that with the trial data, I mean, it's something that we'd have to think about in terms of what the details would be. I guess the concern would be, you know, how well do we -- how strongly do we believe that these data can predict how the results will translate to clinical -- to treatment effects on clinical outcomes and how suspect are we of the modeling assumptions. Those would really be the issues to address.

DR. DUDLEY: And just to follow up, if I can. So I suspect that that's all in sort of the secret sauce of the weighting exercise here about how much do you weight. Is that correct? You can sort of control -- I think, Kert, you said you can control how much you're going to borrow I think from these things. Is that what will happen, is that we'll sort of throttle that a little bit by deciding how much we want to borrow from that?

DR. RUBIN: Exactly. That was the last

point in my last slide, was that it's not so much Bayesian versus frequentist. It's how much weight do you want to give when making a decision to modeling of data other than the randomized --

DR. DUDLEY: So let me try this one more, just if I can -- and I'm not looking for any -- you know, I'm just -- this is just sort of idea sharing. So one might say then that based upon an a priori -- when we're designing a small trial, we might be able to come to an agreement and say here's my PK -- here's my nonclinical PK/PD data or here's what I've learned from Phase I and nonclinical.

I'm going to propose that I borrow some of this information for my prospective, smallish trial that we're going to do and we might come to an agreement prospectively that says how much weight or how much borrowing we're going to be able to do, sort of in a prospective way so everybody kind of gets comfortable that we're not going to put our thumb on the scale at the end of something like that. Is that one possible way of doing this or --

DR. RUBIN: Pre-specification is always good

and would be needed for this type of analysis. I just can't give you an answer yet on --

DR. DUDLEY: But that might be some way of kind of thinking through how you can pre-specify. Maybe --

DR. COX: Okay. Either Aaron, are you on the same topic, because Tom, I'm guessing yours is a follow-up.

MR. DANE: You go first, yeah.

DR. COX: Go ahead, yeah.

DR. LOUIS: I just want to make sure -- I don't think we should be pre-specifying the weight. I think we need to -- and Kert emphasized this. We should be pre-specifying a model that includes a between study or a between body site or a between whatever it might be variance component that the data help estimate and not automatically, but with pre-specification of the structure, allow the data to say should it be given a lot of weight or not much weight. I think pre-specifying the actual weight is a dangerous idea. Pre-specifying a model that will adapt the weights is the right idea.

DR. RUBIN: Sorry. I misspoke. I concur, pre-specify the model.

DR. VIELE: Can I -- one to quickly add to this -- we've designed studies where we have specified in advance if the data matched up your prior expectation exactly, we'll weight your prior expectation 25 percent. But if they don't, then they weight at zero and it's dynamically -- you know, once you've programmed the airplane, it goes on autopilot and it decides the weight based on the results. So you've pre-specified exactly how you're going to determine the weight. But the weight is not fixed.

DR. COX: Okay. So I've got Aaron, Paul and John. Is it a direct follow-up or --

MR. DANE: Yeah. So mine was to that question --

DR. COX: Okay. Aaron, you've been patient. So, please.

MR. DANE: It was something that I've looked at before about can we use the PK/PD as a prior. And I guess to this point that it should be data-driven in some way, and although it's data, it's not the same

endpoint. It's not even patients necessarily. So it's more challenging. So does that say you ignore it? Maybe not. But it's probably the strength of it that you actually alter in some way.

And then, that does get to this idea of rather than pre-specifying the weight, but what you probably want to do is say, well, okay, we have an approach we're going to take and then we look at various scenarios under simulation or something where we say, well, what would it look like at the end so that we could all be comfortable that it makes sense. But I guess in summary it just felt like it was more challenging here because you've got to make that leap from the PK/PD data to the clinical data to construct a trial that just makes it more challenging generally.

DR. COX: And then, Paul?

DR. LOUIS: I'll let the speakers -- yeah, it's challenging and yet I think the benefits, in at least most cases, are worth it. But there may be situations where it's so complex at the moment, without understanding of the science, the biology and so on, that it's not ready for that, but maybe it's

not yet ready for any other analysis either. It's not clear.

MR. DANE: But one thing you could do is -- you could -- yeah, even if it's not -- yeah, this concern here that this probably is too strong, you could even limit the less feasible type responses from the PK/PD which gives you a bit more information, even if it doesn't take you to somewhere like this. So it at least makes it more feasible than it is otherwise.

DR. COX: We'll go to Paul, and if there are folks in the audience that have questions, please start working your way up to the microphone. Paul?

DR. AMBROSE: Hi. Maybe it'd be easier to work the preclinical data in if we think of it in terms of exposure-response in the animal system and an exposure-response analysis of the human data. Oftentimes we can drive dose really low in the animals and get tons of failure of course and very high -- higher than we would in people and we can begin to see a plateau of relationship.

But I think if we were able to take a clinical data set, maybe one from a program or two

that had a problem, and get a good Bayesian exposure-response analysis incorporating the animal data and it gives you a y-intercept so it tells you something about the no treatment effect, right, as drug exposure goes to zero and the plateau of that effect and magnitude of factor and some confidence bounds around that, it'll give you that. That'll help you decide how power -- or how many patients should be enrolled in the study.

And also, for a given regimen or for a given drug regimen, it will tell you how much efficacy is being left on the table, right? The dose worked or it barely worked or it kind of didn't work. But how much -- how much room do I have to bring it up and get more effect out of that regimen. So I think maybe incorporating into -- all into an exposure-response type analysis might be something to think about.

DR. COX: And John?

DR. REX: So I want to be sure I heard something clearly because Mike asked a question that I think caused Tom and Kert to talk about different ideas. So Mike's question was before I do my Phase

III trial, I have some PK/PD or other information that tells me that I believe that I think that this exposure is going to work. And Mike said could we agree how we're going to weight that. And then, the debate that went back and forth here was is that Kert said, well, yes, you could. Tom said I wouldn't pre-specify the weights. But I think you may have been thinking about if I did three different body sites and I don't want to pre-specify the weight across those.

Go back to the case of I'm going to do -- it's like this one right here. I'm only going to do one site. Ignore the fact there isn't a site here. But I'm only going to study nosocomial pneumonia. It's the only -- one indication. I get one result. So the only thing I have before I do that is my prior belief from PK/PD and anything I've generated at Phase I and Phase II that there's exposure, everything that I can figure out that tells me I think I could work in the long -- and then, I get one clinical trial result.

So would we agree -- so because I think we're talking about two different things and I -- because there's something potentially very valuable in

here in using some of this weighting in advance if we could really agree to do that because it's actually potentially a way to buffer against heterogeneity in small populations. And I'm sorry that's a complicated question. So I can either draw it out. But that -- were you guys talking about different things? Does this make sense, that you were talking about weights across individuals --

DR. LOUIS: Let me start first by saying I'm still suffering a little bit from jet ears plugged. So I don't think -- I clearly didn't hear his question accurately because I think for the PK/PD, importing whatever you know for the current study --

DR. REX: Once.

DR. LOUIS: -- I would probably give it, if not 100 percent weight, unless there's some competitor that I could use, I would give it 100 percent weight. I was answering a question about in the outcome endpoint side of things, priors for the treatment effect or whatever it might be. And so, I think I answered correctly, but the wrong question.

DR. REX: Okay.

DR. LOUIS: But take my point as being a point that's valid but not necessarily for the question that he asked.

DR. REX: Well, so one of the things that comes up in tomorrow's discussion is the problem in smaller data sets when movement of a single patient from one category to another causes you to go crazy because all of a sudden you've drifted over some magic margin or confidence interval limit. And it could be that a Bayesian prior would allow you a little more buffer in a really small program. The problem in small programs, how do you get enough buffer against the stuff happens problem.

MR. DANE: So I think it's probably important that Ed suggests -- you know, there are different ways we can apply this. So one is the way Kert was talking where you're borrowing information across body sites, all in patients, all at the same time and that might be quite different from what we do when we're using preclinical PK/PD information and have to make this leap to a different endpoint.

But I guess the common principle is this

idea of dynamic borrowing means that to some degree it's driven by the amount of similarity you have in the historical data or the prior data and what you have. But what you can do is then try and understand how that's going to look. So you can -- to some degree, you can limit how strong that prior is going to be, you know, by the uncertainty you impose on it.

But also, then that's when you can start to look at different scenarios at the design stage and then make sure you're happy with what you end up with. You know, since it's to ensure that the prior doesn't overrule the data or something like that. So a lot of this is possible. It's just being clear when you're setting it up that you have to know how it's going to look and then it's not going to undermine all the conclusions at the end.

DR. VIELE: At the risk of perhaps saying something different again, you're talking about tiny, tiny, tiny sample sizes with your last question. So I think that becomes a qualitatively different problem. If you're talking an example like Dan was giving, there's a lot of control data that can bring to bear

on your --

DR. REX: [Inaudible, off mic.]

DR. VIELE: Right, yeah. So we're talking if you're smaller than that, the nice thing about any kind of dynamic borrowing is the ability of the model to make an assessment over are the assumptions valid and adjust to that. When you get down into the sample sizes as small as you're talking about, you know, three, four, six patients, there's not enough data to assess that.

And I think -- I'll let you weigh in as well -- I think at some point if you're going to weight prior information at all, you have to come up with some weight in advance. And you need to understand your study well enough to understand the risks. But I don't think you have enough information to dynamically assess that during your study. And then, it's a question of the Bayesian methodology that's intended to bring in all the information. But if you've made an assumption that's wrong, it's going to lead you in the wrong direction.

DR. COX: And then, over to the microphone,

if we can. Thomas, did you want to follow up immediately or --

AUDIENCE MEMBER: Yes, I --

DR. COX: Okay. To the microphone?

AUDIENCE MEMBER: Flick Gabray [ph] transcript. I have a question in that really what we seem to be doing here is we are going from a homogenous group into a heterogeneous group potentially even when we're looking at very small sample sizes. And I would like to go back to what Aaron said earlier on about matching and case controls because a lot of the data we have from PK/PD and from our early data is from very homogenous patient sets and our biggest challenge, even with the modeling, when we come to Phase III data is however much we drill down in our multiple logistic regression, we often end up with very small numbers of patients.

And we did a study back in the '90s in SmithKline looking at the impact of some of those confounding variables on the outcome of infection. And it was much greater than the impact of the antibiotic. And Helen will identify with this,

relating to the endocarditis study, and we go back to Ed's issue right at the beginning around how in serious bacterial infections the confounding variables become more of a challenge and the much more difficult to identify into putting them into our prior analyses.

So I wonder whether you have in small data sets a way of dealing with this. I work a lot in drug safety and in very large data sets we have means of dealing with it. But in these kind of small data sets, how do we deal with these very big confounding variables like patients who have COPD in HAP compared to those who are relatively -- have relatively fit lungs?

DR. COX: Any takers on that one? Aaron?

MR. DANE: Only to say my suggestion of matching relies on there being a data set to match to, which we haven't got at the moment. So that's probably a much longer term aim that would have to come from a network in many years' time because at the moment we are struggling to find external data to try and put what we're finding into context.

AUDIENCE MEMBER: Well, with the -- just to

come back to that, with -- there are programs in HAP and so on that we've already entered many patients into who have HAP. We could go back and look at those data sets. The agencies could go back and look at those data sets and we could understand the impact much better. And I think we haven't been good at looking in those data sets to understand the impact of comorbidities which might help us to be able to analyze much smaller data sets more effectively.

DR. COX: Thomas, did you want to follow up?

DR. LOUIS: Just a partial answer and that is that you have -- for all of these, I think we have to think of it in the context of as compared to what. And what I mean by that is the Bayesian approach isn't going to be magically solving these problems. But the non-Bayesian approach or set aside Bayes isn't going to solve them either if you have lots of complications of heterogeneity of patient attributes but essentially no data, then you have to do something.

And at least for me, a strategy of having a discussion about if there are any data that are relevant, build a model with those and build in it the

opportunity for people to be individualized as data or as a group of people to be individualized as information builds up so that early on -- and what I mean by that is early on either in a set of studies for one individual or as data accrue for individuals -- you'll be using as your curve or whatever it might be the -- whatever your best guess was a priori.

But you will then, as time goes on, be giving more weight to the direct evidence as the direct evidence needs less help. And this is part of that dynamic weighting where the model gives the opportunity for the direct evidence as it becomes more stable to be given more weight. And I'm not saying in this case you described this is going to be magical because if there's no information, there's no information. But it's no worse than having no Bayesian formulation and it may be a little better if you can even just have expert opinion give you a good start if that's all you've got.

DR. COX: Okay. I was going to go to John.

DR. TOMAYKO: Yeah. Thanks, Ed.

DR. COX: Yeah.

DR. TOMAYKO: John Tomayko, Spero Therapeutics. I have two comments, kind of related. First, as a former sepsis researcher, I just sort of -- I like this idea of matching that Aaron brings up. But I think about what happened in the last 10 or so years with sepsis, which is pretty amazing actually. You know, Xigris comes on the market for a short period of time and they start surviving sepsis with this mandate of reducing mortality in severe sepsis by 25 percent over five years. And I was sitting there when that first came out thinking, wow, that's a pretty tall order. I guess they really think this Xigris stuff is going to be great.

But it wasn't necessarily the Xigris because it came off the market and they achieved it just by getting us to pay quicker attention and more diligence to starting antibiotics and doing source control, managing the ventilator appropriately -- even though that's been somewhat controversial -- and a number of other kind of standard of care-type approaches. So that's a pretty hard endpoint and a really important to me lesson of how much we could really predict, how

much heterogeneity is out there and how much could we really control.

But then, the other thing I wanted to maybe ask because I agree, Dan and Kert's talks were really great, what's the kind of -- how do we judge -- you know, what's the measure that we're going to judge on or agree that this is the right prior weighting we should give. I mean, there has to be some sort of formula, and I'm going to stick my neck out and say, you know, we're always concerned about type one error. But I don't understand how you're going to handle it, what does the context of one type of error mean, means change somehow when you weight things differently or what's -- so could somebody help me understand that point?

DR. VIELE: I'll definitely take that one. So I think that's an incredibly important question and a key thing that happens when we design trials in this way, we don't want to change the definition of what makes a good trial. The goal -- I mean, so issues like type one error, power, to the extent that they were valuable yesterday, if you switched the design,

you can evaluate it. I certainly didn't show them.

But we have -- we have type one error rates for this design. You can see situations where it reduces type one error and situations where it raises it. And you can weigh how often that happens. But we would assess these kinds of trials the same way we would assess any others, which is given a certain treatment effect, what is the probability that you make the right decision. We may, as we go forward, want to adopt an approach where we are maybe a little more utility patient-centered, you know, what proportion of the population do we treat well. That may be possible.

But we could assess a frequentist trial or a Bayesian trial by that same way. So in effect, we perform the same calculations. And so, I mean, one -- I didn't show it, but largely this sample size savings comes about by being able to get the equivalent type one error and getting more power out of the design and then being able to reduce the sample size. So definitely don't want to change the definition of what makes a good trial.

DR. COX: Okay. Well, why don't we do this? I know there's one person over here at the microphone and there was another person there and if your questions have been answered, that's fine. But let's go ahead and take a break. We're at 3:16. We were supposed to go 3:10 to 3:30. So why don't we go until 3:35 and then we'll come back and the person at the microphone over here, we'll start with you at the next session. You'll help kick us off with the next portion of the program. Thank you very much. See you at 3:35.

[WHEREUPON, the foregoing went off the record at 3:17 p.m., and went back on the record at 3:43 p.m.]

DR. COX: All right. I'll ask that folks move towards your seats. We'll get going here in just a minute. And maybe while folks are moving towards your seats, out at the registration table, you'll find a copy of a case that we'll discuss tomorrow as part of the workshop tomorrow. So you may want to grab a copy of that and read it tonight. It's fairly complex. And thanks to John Rex and a group of others

that contributed to putting that together. It's meant to be a challenging example to help illustrate some of the issues that need to be worked through if you have a drug that targets a single species and that species occurs relatively infrequently.

And just so folks know too, the slides from today -- and I believe the case that we'll talk about tomorrow -- are posted on the Web and on the back of your agenda, you'll see the Web address if you want to find those materials. I'm not sure if things -- I don't think things are up for tomorrow yet. But --

DR. NAMBIAR: For tomorrow they are.

DR. COX: For the slides?

DR. NAMBIAR: The slides are --

DR. COX: Okay.

DR. MARKS: A fair bit of tomorrow's stuff --

DR. COX: Well, I think everybody's slides except my own are up for tomorrow.

DR. MARKS: The intro material is up.

DR. COX: But you'll also find slides there at that same website and after I get mine, I'm sure

they'll be up there too. And I think that's it for the announcements. And folks are back, so that's good. And I think at the microphone over here just before we broke, I think Todd Black, from Merck, had a question for the group. So, Todd, go ahead.

DR. BLACK: Yeah, so earlier today we were talking about how best available therapy can evolve very rapidly. So I'm just trying to understand in the context of a platform-type study, if we're going to be doing this, you know, longitudinally over time, how do we account for then those potential differences in the control group, and I think also in the context of what we just talked about in the colistin example, it was really about trying to modify our understanding of the control response rather than the treatment response in that case. So you know, how do we bring a Bayesian component into that when it really could be truly due to an evolution in the population in the control set?

DR. COX: Does anyone want to try and grab hold of that one? Kert?

DR. VIELE: I'll start. It's a little bit traumatic to a trial when the control arm changes.

This certainly has happened to I-SPY recently with I think pertuzumab, which it's going through that kind of change. If you're talking about a trial network, there are some advantages, especially if the new drug -- if your network is large enough that the reason you're changing control arms is because of a drug that was in your network, you have the particularly nice setup where you already have data on that drug within your network.

So you can do it a little more seamlessly. But there's absolutely going to be challenges. I'm not sure they're any more challenging than starting new trials with that. But certainly you'd have to make adjustments and you'd have to update -- you know, update forms and everything else that goes with it. It's an uprooting experience, but it can be -- it can be accomplished.

DR. RUBIN: I would say that -- oh, sorry -- that the ability of a platform trial to anticipate and plan ahead from when one of the arms may become the standard of care and change the control group is actually a big advantage of studying drugs in a master

protocol and being able to prospectively plan for those whereas if separate sponsors are conducting individual trials and not knowing when a different sponsor may win or when the standard of care may change, that that would be something that would be harder to implement.

DR. COX: Okay. And Aaron?

MR. DANE: Yeah, and I would just add the Bayesian component to that is probably less of the issue because this is true whatever analysis you're doing. If that happens, you've still got to handle that same problem that, you know, halfway through certain comparisons. But as Kert said, you know, you can handle that with the data you're generating as an externality in that study.

DR. COX: Okay. And then, over here at the microphone -- and just so folks are aware, at 3:30, we're supposed to have public comments. So after this question at the microphone, if there's anybody who wants to make public comments, we have a little session then and then we'll go back to the discussion after we've completed that. So please introduce

yourself at the microphone on my right.

MR. WEBBER: Yeah. My name is Frank Webber. I'm an independent consultant from Europe. I want to come back to Dan's wonderful case. What I saw on the chart is a mortality rate of 50 percent -- what I saw on the chart was a 50 percent mortality rate in that infection. And given the statistics he gave us, to bring it down to 40 percent, you would need 385 patients for a superiority trial. And I think everybody admits that 385 patients in such an infection, to show that mortality is a no-go because it's not recruitable. It's an 800-patient study. And everybody I think would admit that going to 40 percent mortality in that infection would be an advancement of care. And the question then is how much more are this panel or the FDA willing to accommodate Bayesian borrowing to the control group to allow an augmentation treatment to get down to 40 percent and have an approval of being an effective augmentation of colistin or whatever.

So in other words, colistin, having 50 percent, the erratic add-ons not being much better,

but a new drug would give you 40 percent. How would you try to develop that drug and what type of statistics would you allow being borrowed from historical control groups, matched control groups and perhaps from the active arm through a Bayesian approach.

DR. COX: You want to do that one Aaron?

MR. DANE: Well, I won't speak -- I mean, Kert's done a lot more on this than me. But this comes down to this question of whether you can use external controls, I think, could help to some degree. So if you're in a situation where you've got some recent trials that are conducted in a similar way, then you could borrow some of that information and, I mean, I know Kert's done some work on augmenting control designs which do borrow that information in some way and reduce the burden of the study. I don't think that's going to help us when we're talking about 40 or 50 patients. But it may do when we're talking in the 100 or 200 patients.

DR. RUBIN: Yes. An intervention that reduces the mortality rate from 50 percent to 40

percent is kind of an interesting example because, on the one hand, it would be a very major benefit in terms of saving the life of 1 out of every 10 subjects in terms of number needed to treat. But on the other hand, the sample size tables show that the randomized trial would become very difficult, but also the treatment effect of 50 to 40 isn't so large that in a nonrandomized comparison you wouldn't be worried about confounding and whether selection effects outweigh treatment effects. So I think that's kind of why we're talking about this today.

DR. COX: And John Rex?

DR. REX: So the generalized question, as I heard it, was if the mortality for your best therapy is 50, 60, 70 -- sorry, excuse me, if the survival -- if the mortality is 50, 40 or 30 and you want to show a reduction by from 40 to 30 or from 40 to 20, right -- so that's the question -- by adding something on. And your question was not about a different therapy but about an add-on. Is that correct? It was about a --

MR. WEBBER: [Off mic] -- replace what you

have with colistin, you have already to go to this -- [off mic] -- leave out colistin, take my new drug and the --

DR. REX: Okay.

MR. WEBBER: [Off mic] -- it doesn't address unmet medical need. If the patient is dying -- how about when the patients are dying and I think the unmet medical need is getting down.

DR. REX: Right, so --

MR. WEBBER: [Off mic] -- you do it in heart failure. You do it in oncology. You do it -- I know you augment as long as it's tolerable and then you'll have incremental benefits, whether you're --

DR. REX: Right. So it's really important to separate the case of augmentation, as you're saying, standard of care versus standard of care-plus as opposed to new drug versus old drug. So the case of standard versus standard-plus, you phrased it as if the question was what will the FDA accept. I'm going to argue that that question is incorrect and that it's not -- you know, what the FDA accepts or not is, in a sense, irrelevant. If you can't -- if FDA approves

it, if it's available on the market, you still have to go to a payer and say, all right, you should pay me $10,000 for this and they're going to say why, show me why.

And if your answer is sort of a collection of sort of stray bits of data that you assemble into an argument, you're not going to get your $10,000. You're going to have to show on something that's really, really clear why you should pay on top of. It's different from instead of, A versus B. It's different from A added onto B.

And I think it's really important to be aware of that. You know, we're doing pricing and payer arguments around the world right now and I can just tell you flat out that you're not going to get anybody to reimburse for an add-on unless you have some very strong data to say why you need to do the add-on. And in cardiology, they do that. You know, you generate large data sets. So you know, I'm just telling you the reality as I have faced it in, you know, recent days, weeks and months.

DR. COX: Yeah, and maybe just to follow up

on it, I think, you know, people, patients, everybody in general would be interested in a drug therapy that can reduce mortality by, you know, 10 percent. I mean, there's no question about that. And I think really what this workshop is about is how do you work through some of the challenges that are faced in demonstrating such a finding.

And you know, we talked some about this at the break. You know, this point in time where colistin might be best available therapy for some patients we hope is time-limited. And you heard, you know, some experiences with trying to show superiority. It's not easy. So I think that's why we're talking about some of the options which you might utilize here, whether it be, you know, trying to study the drug in non-inferiority setting where you can understand its safety and efficacy, the trial's feasible. You can gather some PK data. Maybe you can enrich for some sicker patients and that might be a pathway to study for a drug. When you've also heard some of the discussions about, you know, Bayesian approaches, how you might use them.

So I don't know that we can specifically answer your question. But I think that's what we're trying to get at here today, which is, you know, what are some of the feasible approaches. How can you actually, you know, develop this drug, study it in a way so that it can be available to patients.

Other questions, thoughts on this particular issue? And then, we'll open it up for the public comment period. And maybe I'll just move towards that. Is there anyone who does want to make a specific public comment at today's workshop? If you do, I will pause for a minute as you start making your way towards the microphones. Everybody can just take a deep breath for a moment.

PANEL DISCUSSION 3 (COVERING ALL TOPICS)

DR. COX: Seeing no takers, I guess we will move on. Any questions that folks want to pose, either on the panel, topics for discussion? Lynn, you've got a question. But I -- at the -- nope, you're just working your way towards the seat or did you have a question at the microphone?

MS. KEANE: No, I was ambivalent about

whether I wanted to ask it or not. Anne Keane from Achaogen --

DR. COX: Just please get a little closer to the microphone so we can all hear you.

MS. KEANE: Okay. Anne Keane, from Achaogen. Dr. Cox, in the beginning of June, you were at BIO and you had made a comment that if the LPAD legislation passed, the division would feel that that would give you greater flexibility to approve drugs for rare, very serious pathogen studies, that it would give you more flexibility because you'd be able to take into consideration the risk-benefit of the drug. And unfortunately, as of today, from what I've heard, the LPAD legislation is stuck, made it all the way through the House, made it all the way through the Senate subcommittee and now it's attached to an innovations bill that Patty Murray is holding up unless she gets a guarantee of $8 billion a year for NIH. So it may go nowhere.

So what I'm wondering is given everything that we've heard today and kind of acknowledgement I think from most people that there is an unmet need,

that these patients have a very high mortality rate and there are lots of creative ideas about things that we can do moving forward, but those ideas are all going to take years probably to come to fruition, and there is subpart E regulations which talks about using the broadest regulatory flexibility when you're reviewing NDAs for drugs, for patients with severe, life-threatening infections, instructs FDA to consider risk-benefit to allow greater uncertainty and also gives or suggests at least that FDA work with sponsors to agree on post-marketing commitments that could collect additional data to increase the knowledge about the drug and the risk-benefit.

I'm wondering if in the absence of a functional Congress if FDA can rely on the existing regulations that give you that flexibility and in particular in settings where you have a pathogen-focused study in the setting of a separate randomized control study in another indication.

MS. BORIO: [Off mic.]

[Laughter.]

DR. COX: All right. So maybe I'll just

tell you a story. So -- yeah, so without, you know, commenting on any particular, you know, pending legislation and that sort of stuff in any sort of direct way, so the question that Anne asked me when I was out at Bio was, you know, if LPAD doesn't change the standard, then what does it do for you. And you know, we talked about some of the tools that LPAD has within it where, you know, there'd be premarket review of promotional materials, a designation of, you know, a product as an LPAD product so that people would understand there was a greater degree of risk or, you know, greater degree of uncertainty and/or risk associated with a product and that that, you know, probably would impact upon, you know, how folks utilize the product out there.

So it gives us maybe a little more -- it gives us some tools to give us some of the potential risks and/or uncertainty associated with a product. So I think now you're asking me, you know, how do we deal with this, you know, situation where, you know, we're dealing with unmet medical needs and, you know, there may be products out there where there may be

greater degrees of risk and uncertainty. And I think, you know, what you're seeing and hearing today is we're really trying to work the best we can within the tools and situations that we have, you know, to be able to gather the evidence to understand how these products worked, how these products work as best as possible, you know, will -- I think you've heard some ideas here.

And you know, clearly when we think about product development -- and you'll hear this also tomorrow too, and that is that there really do need to be, you know, achievable pathways so that the drugs that are out there can be developed. You know, patients, you know, need new options now. We know they'll need new options in the future. And you know, we'll continue to try and take, you know, a science-based approach and do the best that we can with the tools that we have available to us. So maybe I'll stop there and hope that that's given you some insights into your question. David?

DR. SHLAES: Yeah. I actually want to go back to the discussion, if I can, and leave LPAD,

between -- with Mike and pharmacometrics a little bit, just to try and expand on this and maybe, Paul, you can help with this. But this is something we actually talked about I think back in 2012 or so, where the idea was, for example, with meropenem, to take a practical example, you have a target attainment of 90 percent or something in most patients. Is there -- if you could then reduce that to what happens in patients with Pseudomonas infections, in patients with VAP and you could look at what happens with a Pseudomonas MIC goes up to eight, you would get then a predicted control response level which would -- which -- and the question is how robust could one make that in terms of using it to establish or contribute to a dataset of external controls for the kinds of things we're going to be talking about tomorrow. So I guess that's --

DR. AMBROSE: Sure. Most of the clinical data sets, since many of the drugs don't -- are not frank disasters, right, there's not lots of exposures that approach zero -- our confidence bounds on those relationships get quite wide as we go from the upper asymptote down, the exposure-response function. And

that's the -- that's the main problem with those relationships. And that's why we've, you know, done things like bring in the preclinical data to help inform that slope. But that's been the problem with them.

DR. SHLAES: Yeah. Okay, so the answer is that the existing data, including the PK -- sparse PK from the Phase III trials does not provide enough -- a robust enough dataset to really use that way. Is that right?

DR. AMBROSE: At least in individual trial. I don't know. Maybe you could do something by looking at a bunch of different trials.

DR. SHLAES: Multiple trials. Yeah, that's -- so something I've asked the Agency. I mean, have you guys ever tried to look back at those data in the -- because, I mean, you have access to all the data.

DR. COX: Yeah, so we have. I don't know if any of our clin pharm folks are here. But they have looked back. I mean, it's come up in the area of pediatrics in particular, where, you know, we've tried to go back and look at the data. And I think that

sometimes the data that we have is not what people think we have. And it hasn't been quite as rich a resource as we might have hoped that it would have been. But we have tried to do that, particularly in the area of biothreat agents. So you know, we may not have quite as much as you think we have. So, but we have tried. We have tried to do it in some areas.

DR. MARKS: I think John wanted to go next.

DR. REX: So that question made me ask -- made we wonder about the question of is there a generalized framework under which you approach the question of constructing a Bayesian prior. And you know, like in benefit-risk, there's these semi-quantitative benefit-risk analysis tools that are supposed to help you at least document your reasoning as to how you get to, you know, conclusion X. And it feels to me like one of the issues with the Bayesian thing, or Bayesian prior is that at some point it involved making a choice. You know, is the number 65? Is it 62? Is it -- you know, what's the shape of the prior.

And I'm just -- is there a general approach

to that that has ever been developed? You know, how is it done such that everybody, you know, understands the tradeoffs that went into it and the documentation of same and sort of does it the same way the next time for a case that's got some of the same features? How do you do it?

DR. LOUIS: Good question. The answer, I think, is both yes and no. The yes part is that there's a fairly developed literature on eliciting prior opinions, not necessarily based on empirical evidence; possibly so, but a process to have a group -- either an individual or a group or individuals come up with their individual priors and then decide whether you're going to simply do a mixture of those or take each of them on their own and do a sensitivity analysis. But the process for doing that is pretty well developed, not that there isn't work that can be done.

For empirically based priors where the information -- excuse me, the opinion part may be mostly on what data are relevant, Dan and Kert may have something different to say. I don't think it's

very well formalized, any more formalized than our using those same data sources to decide on the design of a study in terms of baseline rates, this, that and the other thing. So there may be some general principles. But I don't know of anything that could be approximating an algorithmic approach. But I'll turn it over to the other side there.

DR. VIELE: I think the answer for us is largely no. What we tend to do in practice when we design trials is we may elicit. But more than likely, we look at the available stuff and we do custom priors for each individual project. So I know of no piece of software that -- I mean, there are pieces of software that will elicit priors, but will not design a clinical trial for you. What we tend to do is to try to stress test our designs in a lot of detail. And essentially we go back to operating characteristics. If we use this prior, here is how well it works under a variety of assumptions.

So if your prior belief accurately reflects the world, here's the advantage that you get from using the prior because it's giving you good

information. If your prior doesn't match the world, here is the risk that you are taking by incorporating that prior if in fact it is wrong and it becomes a risk-benefit to the sponsor of I know under what situations I'm going to get a benefit from using this prior and I know under what situations I'm going to take a risk. And then, it's a question of how much do you believe it.

DR. REX: Are they using expert elicitation in any of the I-SPY, lung map, any of these platforms? Do they put that in place up front or is that a strength or a weakness of platform trials to be able to do that?

DR. VIELE: I-SPY -- I should be careful. I don't know every detail of I-SPY. But by in large, I-SPY uses non-informative priors. And it is Bayesian from the standpoint that the accumulating data within the trial is used to update those priors. But there's not expert opinion going in up front. It's the fact that after you've enrolled a couple hundred patients, that data is used to update.

DR. LOUIS: If I could, I'd like to use that

to segue to another benefit of the Bayesian formalism, setting aside the issue of priors and in fact sticking with let's say uninformative priors. For both basic and complicated settings, you get to use the laws of probability to make your inferences, and especially for a nonlinear model and so on. You're no longer doing Taylor series and plugging things in. You're letting the full uncertainty percolate its way through the system and frequently ending up with more uncertainty than you would as a frequentist. It's not always an uncertainty win. It's always, or almost always a validity win. And it also is very effective at addressing nonstandard goals. And I'll just mention one.

If you're ranking things, whether it be drugs or small area disease rates, it actually isn't best to simply take your point estimates however you produce them and rank those. One of the nice things about the Bayesian structuring is you say if I only knew those underlying parameters, if I had them in my hand, how would I rank them? Well, I'd put them in a line, small to largest. I don't get to see them, but

what I do get to see is the posterior distribution of them. And I can do what is a nonstandard computation to get the best ranks and the associated uncertainties. It's just one example where it's very hard to even know how to think about that without the Bayesian formalism, not necessarily the Bayesian philosophy, if you'd like, you know.

DR. COX: Yeah, Kert?

DR. VIELE: Yeah, very quick follow-up. In terms of when we say Bayesian methods, we design, you know, a hundred trials a year. By in large, almost all of ours are non-informative priors. We use Bayesian in terms of how to use the data that's coming into the trial as it accumulates more than in the sense of incorporating these extra pieces of information prior to the trial. So there's just another way to use Bayesian methods.

DR. REX: Because I think that in this particular area, what we're faced with -- if you look at the handout for tomorrow, you're going to see there's this hypothetical drug that we've, you know -- it's actually pretty close to some real cases. But

the sense you have going into Phase III is that it does what all other antibiotics do. It seems to kill bacteria and it works in a variety of models in animals and even in a little version of a human being, or sorry, version of a human illness.

And so, you have this belief going into Phase III that, you know, it probably will do something. And so, I guess what you're saying is that there's not a standard way of taking that, the observation that you'll see in the handout and turning it into some sort of an informative prior as opposed to an uninformative prior.

DR. VIELE: I think that in general would be very hard.

DR. REX: Yeah.

DR. VIELE: I think this gets back to what Ed was saying. You know, if there was a long history of here is the data that I had prior to a number of trials and here is how this evidence translated into my clinical endpoint, you could do a lot with that. But I'm not sure -- I'm not sure we're there.

DR. REX: Well, but in fact, those data do

exist because that's the domain of Paul Ambrose. You know, all of that still -- like the little picture you showed just this morning, Paul, of the likelihood of Phase III efficacy success based on where you were in your preclinical PK -- where your actual pharmacology came out on the doses on the exposure-response curve. So in effect, that exists. One of the -- maybe one of the stepping stones.

DR. COX: I think Aaron?

MR. DANE: Yeah. I mean, that starts to inform I guess what we would have to look at is the uncertainty around that and what the prior distribution would look like because the numbers are small, just because there haven't been that many development programs. And it gives some comfort, but I'm not sure how much it would help in terms of an informative prior.

DR. MARKS: Sam?

DR. BOZZETTE: Well, I think it is an informative prior because I think that's what Ambrose's presentation showed us. I mean, it showed us we have some failed programs and when we went back

and looked, there was an informative prior that either people chose to ignore or that we discovered afterwards. So I do think that there are informative priors. I don't think we have a lot of examples -- and we can come to those -- of clinical trials that failed because of sunspots or some unexplained phenomenon in the universe.

I think that's been the lesson over the last few decades is that we've had -- we've learned a lot about doses and we've learned a lot about exposure-response relationships that a lot of these sort of failed trials are rooted in that area where I believe those priors are going to be extremely important in terms of structuring our priors for clinical trials.

MR. DANE: I think the point is, Mike, that it depends whether you want your prior to be elicited or data-driven or empirical because if you elicit it, you can make that comment. But if it's more data-driven or you're using the numbers you've got, that's where there's a lot more uncertainty, because the numbers are small. You know, we haven't got many. We've only got -- I can't remember the numbers now,

but a relatively small number of approvals or failed studies. So yeah, normally we'd ideally want the prior to be driven by the data rather than elicitation, if we can. And there's still uncertainty there just because there's not a lot of data there to do that with in terms of drugs that have been approved or haven't.

DR. MARKS: Sam, we'll bounce back to you, then --

DR. LOUIS: I think the very act of going into Phase III means somebody thinks something good has a reasonable chance of happening. Otherwise, I can't imagine going into Phase III. And it might be the prior. But it might also be the industries' or the government's or somebody's utility that even with a relatively broad uninformative prior, the win would be so big if we got it that it's worth doing. So I think we need to -- can't unlink priors from utilities basically. And some combination of those makes it a good bet I guess is the way to put it.

DR. MARK: One more time, Sam.

DR. BOZZETTE: My prior is that there's a

lot of information about priors out there. And even in -- even in failed trials, you know, there's information in the control arm and especially in the context of a platform trial looking at, you know, informing estimates of the effect in the control arm. It seems to me that there are a lot of studies out there that could be used to do that. So I don't think -- I mean, it's certainly PK but I think clinical data is there.

It's just going to take a specific effort to pull that stuff together. And I don't know if you do that through agency, you do that through -- well, it was mentioned at lunch a big data effort from clinical databases, you know, the large clinical databases or of it's done by a consortium of companies looking at their own trials. But there's an awful lot of information out there on what happens in standard therapy.

MR. DANE: I don't think that needs to be Bayesian. I think we should just do that anyway, irrespective of the analysis approach you're going to take. You know, there's an element of this, well, we

should try and pull together the information we have. And then, we'd get into discussions of what's the most appropriate analysis. But all of that's going to inform whatever we do and however we do it, I would say.

DR. MARKS: John?

AUDIENCE MEMBER: Yeah, I thought that was a nice comment that Sam made, that there's a lot of prior out there. But I also think there's a lot of heterogeneity out there that I worry about. And you know, maybe my memory doesn't serve me correctly. But I think when doripenem came to an ad com, the first time around, it was like a 500 mg three time a day dose and they did what I thought was the first study in VAP patients, theDORI-10 study. And if I recall, they met the endpoint. But there were some issues and we were changing endpoints. It was a clinical cure endpoint. But there were some issues.

And then, they went out and, probably for good reason that wasn't disclosed that I know, doubled that dose and failed to even complete a study because it stopped for futility. So I mean, I don't know. I

know that getting the dose right is important. But Paul talked about augmented renal clearance and I heard about that. You know, that's a hard thing to study ahead of time. Yeah, you could go to an ICU population and maybe do some BALs and whatever. But there's just a lot of variability in exposure that you're going to see in your patients. It's hard to --

DR. BOZZETTE: Yeah, but there are millions -- let me just say there are millions of cases out there, not only -- I mean, if one wants to -- you can look beyond the clinical trials even and look at the large EMR datasets to get some sense of what happens with these patients. And they have things like creatinine clearance and some other things. It's certainly not PK data. But it's things that you can make inferences from, you know, and comorbidity information, labs, et cetera, et cetera. So I think both within clinical trials and in large, you know, EMRs, that there might be some potential. Sorry to interrupt.

DR. AMBROSE: So even with the doripenem higher dose study, right, it was a gram every eight

hours and it was over a four-hour infusion. So the steady-state drug concentration for a four-hour infusion on average for doripenem would be 16 µg/mL. It penetrates about 25 percent of the epithelial lining fluids, so let's just make the math. Should we drop it to µg/mL? And then you throw on 60, 70 percent variability on clearance and volume. You end up with people approaching drug exposures of zero again. I don't -- you know, the dose wasn't high enough. It's just -- it's the variability. It's what gets you.

AUDIENCE MEMBER: But the first time the dose did not -- [off mic].

DR. AMBROSE: No, it wasn't good enough. It didn't get approved.

AUDIENCE MEMBER: It didn't get approved -- [off mic].

DR. AMBROSE: No, it had more mortality. I believe it was with seven deaths in the doripenem arm and one versus the control or some number like that. But --

DR. MARKS: We'll go to the microphone.

DR. BLACK: Yeah, Todd Black, with Merck. So I think just to point out, all the new drugs we're talking about today are ß-lactams, ß-lactamase inhibitors, aminoglycosides. Having done drug discovery now for many, many years, you know, what we would really want, that new agent, new mechanism is really, really hard to come by. It's not for lack of trying. So our only solution in the future may be this adjunctive therapy. So to John's point, that may be where these priors and understanding or how you're modeling I guess the add-on on top of an effective therapy. Does it open up a door for us there to help us do these developments with an adjunctive therapy as a primary, as we, you know, get around all these concerns and questions about combination therapies.

DR. MARKS: And I was going to ask a question about sort of the borrowing piece, to go back a little bit, borrowing across body sites, how comfortable we are with, let's say, if we have good success in intra-abdominal infections, does that help with HAP/VAP? You might say not very much. But if you had success with HAP/VAP, would you weight that

more heavily in terms of trying to support an intra-abdominal infection and how people feel about the different body sites influencing the data more or less.

DR. AMBROSE: I'll take a whack at it. Yeah, I'd feel more comfortable going backwards from HAP/VAP. Why would that be? I think when we've looked at, from a PK/PD perspective, clinical trial datasets, an intra-abdominal infection requires something like net bacterial stasis in the animals. It's a relatively low, low threshold and, generally speaking, those studies are done at relatively modest bacterially dense inoculums, right? The pneumonia studies are done at high bacterial inoculums and, generally speaking, require more drug.

So I do feel that generally speaking, if you can treat a pneumonia, you probably are going to be okay in an intra-abdominal infection, assuming, you know, you're not inactivated in a more acidic environment or something like that. I'd feel more comfortable in that direction than the other.

DR. MARKS: And how about UTI when it comes

to intra-abdominal infections? Because intra-abdominal infections, I don't know, one-and-a-half, maybe two times slower to enroll, a little bit less influence in the antibiotic, more related to the surgical intervention. If you had a lot more urinary tract infections, would you be more comfortable propping up the difficult intra-abdominal infections?

DR. AMBROSE: I think a urinary tract infection, relative to pneumonia, again, is a little bit easier to deal with, most of them anyways than a pneumonia. But are you asking me to rank it versus intra-abdominal infection? You know, we don't have many exposure-response analyses at all in the urinary tract infections. It hasn't been a place that we've done those analyses. My gut instinct is that some -- you know, generally speaking, it's not as high a threshold as ventilator-associated pneumonia.

DR. REX: I'll just add an observation that we had out of the Avycaz program, which was that if you take nosocomial pneumonia, intra-ab and UTI and look at actual physiologic derangements, which one of the three is the hardest on average in that population

to hit the exposure you want, and it turned out that, at least for that combination, intra-ab was actually the hardest. You know, and nosocomial pneumonia was a close second. But intra-ab was really tough.

And I think the logic, the best we could tease it out, was you've got people going to surgery, you've got deranged volumes of distribution in the belly. So all kinds of whacky things are happening with your blood volume. So you know, I guess to answer your question, I think one of the things I got out of that was that intra-ab is -- surgery is a confounding variable. But on the other hand, pharmacokinetically, it's a very demanding setting. I just thought that was an interesting observation. That will be in some one of our papers somewhere, that that fact was observed.

DR. MARKS: Helen, any thoughts?

DR. BOUCHER: Yeah, I would just add that clinically it sort of comes back to something we talked about this morning. I think the inclusion of any group of patients certainly with pneumonia, but also with bloodstream infection, is incredibly

meaningful to the clinician. And that's also in this group where there's a predictable high mortality.

So if we see that the new drug works, that's incredibly useful, especially if the main study is a UTI study, where I know we get the bacteria. We have the potential for statistical testing. But clinically, we're not always comfortable with just UTI data to take it into that much sicker population.

And so, if there's any way to learn that information in a high quality type of study, like a registration type of study, even if it's not the whole study, that's a lot better than relying on a random publication. And I think in the real world, we're often -- that's what we get and we get it two years later, you know, after the approval is publication of cases -- and again, don't get me wrong. That's my business. But the high quality data, the patients enrolled and monitored and studied for safety as well as efficacy in this kind of setting really does have power that's important.

DR. MARKS: Well, let me draw on that a little bit more because some sponsors are going with

the complicated urinary tract infection studies and then jumping to a multi-body site, more drug resistant population. But what's missing in that equation for you and what -- how could they supplement that package to get you more interested?

DR. BOUCHER: I think that, you know, in doing that kind of a thing, really important is going to be the enabling work that enables them to go into those other body sites and, coming back to Paul's work and others, to make sure the dose is correct or is as good as we can estimate. And again, you know, in a perfect world, we'd have the perfect. But this is not the kind of thing that's going to lend itself to perfect. So really good enabling data, really good ability to describe the patients that are treated in terms of diagnosis and in terms of outcome, really, really important. And we didn't get into this today. But again, from Nick and my earlier life with aspergillosis, you know, drugs have been approved on historical controls and that's all about the ability to describe the population in each individual patient to ascertain that they really had the infection, to

the best of our knowledge, that they had a good treatment effect.

DR. MARKS: So on Sumathi's slide earlier this morning, she had cUTI, stroke, cIAI or whatever acronym you used on that slide, as sort of interchangeable, one or the other. Would you prefer one or the other in terms of a sponsor coming to you for running clinical trials? You'd rather have an intra-abdominal infection program rather than a UTI? You want both? You want --

DR. BOUCHER: I mean, again, I think in a perfect world, we'd want it all, right? And so, treating the kind of patients that I treat, I would always prefer to see some experience in the more ill patients. But I could see very reasonable approaches using either. And I think a lot of the pros and cons have been articulated. You know, UTI, you get the bugs. It's a more homogenous population.

So that's a good thing in some ways. And on the other hand, in the complicated intra-abdominal infection, it's a little harder to treat. The patients are more ill. There's more probably sepsis

in that study and things that might, you know, make us feel more comfortable in a population. But that could be addressed in other ways if you did the small pathogen -- the small group study. So I think both could work.

DR. MARKS: So it would be a review point, just to use the FDA language. Sorry. Ian?

DR. FRIEDLAND: So I have a question. I'd be interested in what Helen has to say and what the regulatory folks have to say. And this is also again about prior knowledge. So if you're dealing with a known class, let's say ß-lactams, we know a lot about ß-lactams. We know a lot about the PK/PD, versus a completely new class that has a new PK/PD. Would you be more comfortable with uncertainty when there's like a known class of drug, even if it's a new drug versus like it's a completely new class or are you totally agnostic of the drug class?

DR. COX: So if you think about it, I mean, the question is at least two-dimensional. And so, you're asking suppose somebody else comes in with, you know, another member of the same class. So the level

of innovation there may not be huge. It may offer something that existing drugs don't offer. But it probably, on the benefit side, is not going to be sort of something completely different. So I mean, we would take that level of benefit into consideration. Is it addressing some unmet medical need? What do we know about the safety? And weigh those two things.

Now, the thing that you are contrasting that is a wholly new class, something that operates via a completely different mechanism. I can make good arguments to accept a fair degree of uncertainty around that drug because I'm presuming that it may be able -- you know, it operates via a wholly new class. So it ma, you know, provide benefit in certain patient populations that, you know, may go beyond what you could do with a class modification. So you know, those benefits may be for a particular subset of the population, not for the population at large. But I mean, you can argue these situations both ways.

So I don't know that there's an answer one way or another, specifically what's easier, you know, this way or that way. I think there's -- you know,

each of those two molecules -- and these are hypotheticals, so we don't know exactly what they do -- you know, has the potential to bring, you know, either, you know, different levels of benefit, you know, based on the type of molecule. And then, you know, the other question is what do we know about risk. Sometimes you come into your clinical program with, you know, completely clean animal studies and it doesn't look like it's provoking much of anything. And you know, then it looks clean even in the limited safety database. That doesn't give you guarantees, but it sure, you know, looks like it's not a big problem.

The flipside is suppose that preclinical data -- you know, you're starting to see significant toxicities already and you've seen some of that being reflected in the patients that you see. So it's very hard to answer those hypotheticals. But I've outlined at least some of the things that you might think about as you're looking at these two different types of prototypical agents, something from a new class and something from a wholly new -- or something from a new

class versus a class modification. So hopefully that makes sense.

DR. KARTSONIS: So to kind of segue a little bit more to the safety question, we talked a lot obviously today about efficacy. But -- and I know the original streamline guidance spoke to a sort of specific safety database of at least 300. Has any of that thinking changed or is it still the assumption that it's 300 and is there a modification on that at this point? Just curious on that.

DR. COX: Yeah. So the derivation of the 300 number. So if you do 300 patients and you don't see anything terrible within the 300, the upper bound of the 95 percent confidence interval I think is 1 percent for that zero number. So that's where the 300 comes from. And, you know, I mean, at some point, it's just trying to figure out, you know, how much do you want to know about a drug before it's out there on the market. You know, the 300 number is one that, you know, we've sort of turned to and, you know, I don't know that there's anything magical about it. But it gets you to a certain level of certainty with regards

to bounding risk, you know, before a drug gets out on the market. Are you suggesting we go higher or are you suggesting we go lower?

DR. KARTSONIS: I was just wondering if there's been -- because we didn't touch on it today -- I just --

DR. COX: Yeah.

DR. KARTSONIS: I mean, I particularly think it's going to be relevant as we speak tomorrow about, you know, single pathogen because you may be in situations where you may not be able to get to 300 without --

DR. COX: Right. So you're right. We will talk about it some more tomorrow too. And you know, while it may be difficult to get that number of patients with a particular target pathogen of interest, in the course of, you know, doing what you're doing in your trial, unless you have a really, really good diagnostic, you may be able to gather some safety data from other patients that don't necessarily have the target pathogen of interest. Their course of therapy may not be as long, unless you find out they

have something else, you might stop the therapy. But you may be able to gather some additional safety data.

So you know, it may -- you know, it may be a number that still is achievable within the development program. And you know, if you think about it, you'll have some, you know, multiple dose studies and, you know, studies in patients. So you know, I think it probably is still achievable, even though -- even though, you know, because you're going to be getting data beyond just the patient population with the single species of interest. That's my impression. I'd welcome thoughts from other people on that too, from the experiences you may have.

DR. LOUIS: So I need to do a methodological moment. If you see N events in trials, as long as N is greater than about 15, the upper 95 percent limit is three over N, no matter what N is. Pretty cool.

DR. COX: So did I get the math right?

DR. LOUIS: Absolutely.

DR. COX: Okay. That's good.

DR. LOUIS: N was greater than 15 and three was -- [off mic].

DR. MARKS: Just going back and reflecting on -- I think John mentioned it earlier in terms of trying to work through all the pricing and reimbursement, which I know we don't directly deal with here, but when you think of statistics and how to have these kinds of conversations with payers and we start adding in things like we're borrowing from here, there and yon, I was on a call recently with some other pharmaceutical companies talking to a European pricing reimbursement group, which said essentially you're telling me that this drug is essentially the same as what's already approved. How am I supposed to pay you a premium for that? Now, we're going to have another complicated situation of trying to describe, well, we borrowed from here, we borrowed from there. So I think that'll be interesting times.

MR. DANE: Although some of those payer groups have been doing the Bayesian analysis more than we have in the regulatory setting. So I'm not sure -- there's still to be worked through the assumptions and everything like that. But I'm not sure it necessarily is a huge problem in that some of that's brought in

for some of the indirect comparisons that happen and all sort of other things that tend to happen in that reimbursement setting.

DR. REX: So it wasn't a huge news release. But about 10 days ago, Sweden announced that it was going to engage in a two-year pilot program to test a novel way of buying antibiotics. And the Swedish model is one of simply paying an access fee on an annual basis to ensure that the drug is available. And then, there's -- and they estimate that they will use a tiny number of courses of the drug. But they simply want to know that it's available and that it will be available to them. And there are a couple of drugs that look like they would be appropriate candidates for that pilot. And they've said they're going to figure out how to do that this fall.

And I'm close enough to that to know that, you know, really part of what tips it over there is that the agents have a very clear-cut -- each one of them has a very clear-cut thing that it offers and so, you can articulate it. It's a very clear science-based story. It's an organism that is otherwise

difficult or treats a form of resistance that is otherwise difficult and the data are really reasonably good. And that's why I come around to Mike -- there's another conversation going on in the U.K. about a model that has a somewhat different structure. It's an annual fee that includes a number of courses of therapy. But it's essentially the same thing. It's a market entry reward. And the same things are tipping the balance there is that you've got to be very clear about what you're buying for your money.

And it was -- it's been those conversations that led me to the fire extinguisher analogy to saying that there's just not going to be a lot of interest in the same old fire extinguisher. And that's just a way to articulate what you need to get reimbursed. And so, you know, it's just kind of part of what you've got to deal with. It isn't -- because it's inherent in all of this.

You don't buy a new iPod or a new iPad or a new I-anything unless there's some feature you want that's not in the one you've got, right? And so, I just -- I think it's important to keep that in mind.

And you know, it's also that bit about statistics, only show you what you can already kind of see. You know, that's the -- you know, stats, if you can't already sort of see it with your eye, you're probably not going to believe the stats. So I think that's something else to remember in all of this. We can buff it up a little bit with statistical calculations. But fundamentally, it better be something that you can sort of see in the dataset.

DR. BOZZETTE: I guess I would just say that I'm not sure how diagnostics would fit into the schemes that John has discussed. But we have to figure that out or there won't be the kind of supportive diagnostics that are needed.

DR. REX: I a hundred percent agree and I mention the DRIVE A/B project going on in Europe right now about the value of antibiotics. There is a DRIVE D/X that is just now forming up that is meant to tackle the same problem because I think the reimbursement issue for diagnostics is at least an order of magnitude harder than it is for antimicrobials. And yet, we desperately need you to

make good tests.

DR. MARKS: And the other thing I've figured out is my next career, I'm going to offer a non-informative priors as an expertise. So I learned that.

[Laughter.]

DR. REX: So -- so before we close, could I say something about tomorrow, just real quick?

DR. MARKS: Please do.

DR. REX: There is -- if you didn't get one already, there's a handout on the table outside. And if you didn't -- if you don't want that, you can also download it. If you'll go to the webpage for the meeting, you'll find it with FDA unmet need workshop 2016. That's how I'm finding it on my browser. There's a hypothetical case of a drug called X1 that is a narrow spectrum anti-pseudomonal and a number of us have collaborated on pulling together a story. What you'll be able to download is the preclinical database and a little bit of Phase I and Phase II data and your homework for tonight while you're having your glass of wine with dinner is how would you develop

this. And there's some useful tables provided. What's the frequency of Pseudomonas? But you've got to design a real program. And my target upper limit suggestion for you is within 1,000 patients get this study -- do the Phase III program because that's, you know, somewhere between $60 and $100 million, depending on how you do it, and you might be able to get that much money together to do this. So that's -- I just want to say that that challenge is there. And a fair number of people at the table right now have been involved in kind of turning that into what we hope is a very realistic story. So don't miss your homework. So tomorrow will be more interesting to you if you've done that.

DR. COX: All right. Well, it seems like we've arrived for today. So I want to thank everybody for joining us here today and participating in the discussions. And I think it was, you know -- at least from my standpoint, it was an excellent day with lots of important information imparted and a good chance to talk through a number of issues. Tomorrow, we'll start at 8:30. So get some rest. John's giving you -

- has given you your homework. And believe me, it is quite an assignment and we'll spend some time discussing that tomorrow. So we look forward to seeing you tomorrow. Have a good night.

[WHEREUPON, the foregoing adjourned at 4:41 p.m.]

CERTIFICATE OF NOTARY PUBLIC

I, IRENE GRAY, the officer before whom the foregoing proceeding was taken, do hereby certify that the proceedings were recorded by me and thereafter reduced to typewriting under my direction; that said proceedings are a true and accurate record to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

IRENE GRAY

Notary Public in and for the

District of Columbia

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I, BENJAMIN GRAHAM, hereby certify that I am not the Court Reporter who reported the following proceeding and that I have typed the transcript of this proceeding using the Court Reporter's notes and recordings. The foregoing/attached transcript is a true, correct, and complete transcription of said proceeding.

07/27/2016

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Transcriptionist

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