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## FOOD AND DRUG ADMINISTRATION

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FDA-IDSA-NIH-Pew Public Workshop  
Enhancing the Clinical Trial Enterprise for  
Antibacterial Drug Development in the United States  
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DATE: Day 2: November 19, 2019

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LOCATION: FDA White Oak Campus  
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REPORTED BY: Michael Farkas, Notary Public

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1 P R O C E E D I N G S

2 DAN RUBIN: Good morning, everyone.

3 Please take your seats. I'd like to get started.

4 Welcome to day two of the workshop. We're now

5 beginning our session, strategies to better support

6 antibacterial drug trials. I think we won't go around

7 the table and redo introductions, except I should

8 probably introduce myself since I was in the chairs

9 yesterday and I've jumped all the way to moderating

10 the session along with it. Jan Knisely, who's going

11 to be the co-moderator for today.

12 So I'm Dan Rubin, and I'm a

13 statistician at Cedars. Professor Evans, could you

14 introduce yourself since you weren't here yesterday?

15 SCOTT EVANS: Sure. Good morning,

16 everyone. My name is Scott Evans. I'm a professor

17 and the chair of biostatistics (indiscernible) at

18 George Washington University. And I'm the Director of

19 the SDMC, Statistical Data Metric Center.

20 DAN RUBIN: And do we have any other

21 new people who weren't at the table yesterday? Okay,

22 great. Well, then let's get started. Our first

1 speaker is Dr. John Rex. John Rex is the Chief  
2 Medical Officer at F2G's Manchester, UK based firm  
3 and brings 30 plus years of development and policy  
4 experienced, focused on antimicrobial agents. His  
5 experience puts moving antifungal and antibacterial  
6 agents from pre-clinical development through all  
7 development phases and various roles.

8 JOHN REX: Thanks, Dan, and thanks to  
9 you all of you for being here. And this theme came up  
10 yesterday. This is a pivotal moment in time. What do  
11 we need, what should we be doing, who should be doing  
12 it? And the title of this talk is antibiotic R&D 3.0,  
13 and I'd like us to think about rowing the boat  
14 together and in the same direction.

15 These slides are readily available. I  
16 actually think the slides from the whole meeting are  
17 going to be available, going to be posted, and  
18 obviously, I'll share them via my newsletter.

19 So the pivotal point in time is  
20 fasting. We have poured enormous resources into pre-  
21 clinical and phase one, CARB-X and so forth, and there  
22 is really signs of progress. We are seeing some

1 innovative things deep down in the pre-clinical  
2 pipelines, things that nobody had ever discovered  
3 before. They won't all be drugs, but some of them  
4 will be.

5                   Unfortunately, this whole enterprise,  
6 hundreds of millions of dollars is going to blow apart  
7 due to two intertwined issues: the first is that new  
8 antibiotics are kind of like a bridge to nowhere.  
9 Actually, that bridge on the left, it actually is, at  
10 low tide, there is a path to and from it, but at high  
11 tide, it's just out in the middle of the water. And  
12 right now, it's high and we're drowning.

13                   New antibiotics don't get used. Some  
14 of the agents truthfully aren't that interesting. But  
15 even the good ones are perceived as only non-inferior.  
16 The guidelines are out of date by years and  
17 stewardship is based on cost and utility.

18                   And then on the flip side is that the  
19 payer model is broken. Antibiotics were the fire  
20 extinguishers of medicine, as you've heard, and we  
21 need to stop paying for them on a per-fire basis.

22                   We cannot fix it all at this workshop.

1 The things that are in scope are the types of trials  
2 we can conduct, the types of data we can realistically  
3 get, how those data should be reported in labeling,  
4 how the ID community talks about this data, how the  
5 guidelines and the guidance's should handle this data.  
6 What's out of scope is payer models. And also, I'm  
7 going to say that personally out of scope is, oh, I  
8 just don't like it. Okay? If you don't like it, you  
9 either have to suggest something else that's better or  
10 get with it because you're otherwise keeping us from  
11 going anywhere; it's why the boat is spinning in  
12 circles.

13 So with that rant over -- sorry -- this  
14 thing, big picture. Antibiotic R&D 1.0 was sort of  
15 the dawn of antibiotics to the mid-2000s. It was  
16 generally very easy to see the value in the drugs.  
17 But over time, we were learning about weaknesses in  
18 our pivotal designs, particularly related to upwards  
19 of 20 infections.

20 R&D 2.0 was the moment in time when it  
21 all kind of went back to ground zero. The Ketek  
22 hearings in Congress in 2007 was a period of time when

1 we didn't know how to develop anything; we weren't  
2 sure about it. When we got busy, the f'ing NIH, the  
3 whole process led to rapid refinement of not a very  
4 orderly science.

5           And we now have very clear, very sound  
6 scientific roadmaps for major indications. Single  
7 pivotal trials gradually became acceptable for  
8 approval, and there was a lot of harmonization between  
9 EMA and FDA, and also increasingly recently Japan, and  
10 that's all really good stuff.

11           So what's R&D 3.0 going to look like?  
12 Well, these are the ideas. It's how do we use LPAD as  
13 a springboard, the problems we have to solve, a little  
14 bit about superiority again, and the notion that this  
15 is a community-level activity and some suggestions.

16           So LPAD, we heard that mentioned  
17 yesterday, and Dr. Nambiar talked about three levels  
18 of approvals: standard, limited use, and LPAD. In  
19 truth, there is no distinct labeling for -- there's no  
20 distinct pathway, it doesn't have a name for limited  
21 use; it's just -- it's the agreement that we can  
22 approve with single trials.



1                   But LPAD is a special beast. It was  
2                   created by Congress as part of the 21st Centuries  
3                   Cares Act, and it really ought to be called LPAAAD  
4                   because it's limited population of antibacterial and  
5                   antifungal drug. You'll notice there are least two As  
6                   missing in that.

7                   The concept behind LPAD is that  
8                   physicians and patients will accept greater  
9                   uncertainty for serious diseases with unmet needs, a  
10                  very standard concept, but now codified with respect  
11                  to antibiotics. And it says that, in brief,  
12                  streamlined approaches based on severity, rarity and  
13                  prevalence are what you're going to have to do.

14                  And this means single trials, widen  
15                  inferiority margins, basically being creative within  
16                  certain boundaries because it's not a license to run  
17                  riot. You still have to meet the standard of  
18                  substantial evidence of efficacy based on adequate and  
19                  well-controlled clinical data.

20                  Also, the labeling must make it clear  
21                  that the limited population -- that there is a limited  
22                  population for which this drug is addressed. And this

1 is -- it's important for us that LPAD gives us two  
2 gifts: gift one is the phrase itself, LPAD. This drug  
3 is special. Has the logo been designed yet? I don't  
4 know, but there's going to be something on the box in  
5 a little triangular thing that says this is different;  
6 don't use this unless you understand it and you  
7 understand the risk/benefit around it.

8 Don't use it in just anybody; use it  
9 only in these people. And the package labeling -- I'm  
10 sorry, the label data actually has this phrase right  
11 here, limited population in at least six places on  
12 page 1 of the label, some of them in big multipoint  
13 type.

14 And you combine that with robust  
15 stewardship programs and CDC's ongoing surveillance,  
16 LPAD agents are something that we can pretty much say  
17 to the community, you have to use this right. And we  
18 can -- we should leverage that notion that this is  
19 something where we can tell people, be careful here,  
20 use it appropriately.

21 But that leaves us with some problems  
22 there. R&D 3.0 needs to address two big groups of

1 problems: the first one is communicating the value of  
2 standard NI trials, and I put that one separately  
3 because that's a community-level thing that we can  
4 take on. We have to educate ourselves and our peers  
5 on the notion that a cUTI trial is not stupid.

6           And then B, C, and D all tangle  
7 together; developing for rare or resistant pathogens,  
8 developing for less common infections. And what's the  
9 adequate quanta of data for labeling for B and for C -  
10 - B, C and D are reduced to study size -- and how you  
11 think about that phrase again, "Substantial evidence  
12 of efficacy based on adequate and well-controlled  
13 trials."

14           Nowhere in any order or reg does it say  
15 that that means alpha means .05 and a margin equals 10  
16 percent and a specific end point. None of that is  
17 defined. What we do -- it's up to us to define stuff  
18 that is solid enough, and we can consider risk  
19 benefit.

20           A little bit of a sidebar about  
21 superiority, and you just have to bring this up and  
22 remind everybody about this. Superiority is not a

1 generalized answer. If you happen to find superiority  
2 for a new drug, great, but that instantly resets the  
3 playing field for every subsequent drug. You have to  
4 keep that in mind. If it's -- the core problem is  
5 that antibiotic responses are dichotomous -- cured/not  
6 cured. Very few other diseases are that way. I cure  
7 your pneumonia. There's nothing better than cured.  
8 You go home and have your next 60 years of life.

9           And if it's easy to run a superiority  
10 trial, actually something bad has happened in public  
11 health resistance must be common enough that I can put  
12 people in an arm where there wasn't a good choice.  
13 And except for the mildest of infections, superiority  
14 means that not only somebody got hurt, somebody  
15 probably died and did not really need to die if we had  
16 an appropriate drug.

17           So we actually want superiority trials  
18 to be impossible. If it's briefly possible due to a  
19 gap, the first successful drug closes that gap and  
20 makes it hard to go back to doing more superiority.  
21 So we all have to know this and we have to teach it to  
22 ourselves and teach it to our colleagues: non-

1 inferiority is our main tool; they're sensitive to  
2 drug effects. Modern designs work really well, and we  
3 have to be very clear about this.

4           And this segues into the notion this is  
5 not just a regulatory problem. It's easy to be  
6 critical and ask, why is it you say it's nothing; oh,  
7 it's just a cUTI study. What it was, because you  
8 actually want more data. We talked a lot about a lot  
9 this, I wish for more stuff. Academia and the journal  
10 letters say, well, you did this resistant pathogen  
11 study, but it's too small. And the payers say, I  
12 expected superiority data in the label. And  
13 physicians say, I'll wait for the guidelines to  
14 change. And the patients say, non-inferiority sounds  
15 so dodgy; I don't know what it really means, but it  
16 really sounds awful and my doctor doesn't like it.

17           This is all a communication and an  
18 education problem as we've just been discussing.  
19 People don't understand the core scientific  
20 principles. Why is it that some non-inferiority  
21 trials are rubbish? We have done NI trials and  
22 published them in the past and they were rubbish. The

1 ones we do now are not rubbish. There's a reason for  
2 that change.

3 Non-traditional agents. We got  
4 somebody at the table today who's interested in  
5 bacterial phase. There are a variety of other non-  
6 traditionals we'd like to have developed. They face  
7 the same problems. We actually -- if we're going to  
8 have any of these new toys, we're have to deal with  
9 those, so here are my suggestions.

10 The first one is: we, as a community,  
11 have to become cognizant of the labeling regulations.  
12 You need to take the words on this slide and laser  
13 etch them on the inside of your eyeglasses so that  
14 you're constantly looking at them and are aware of the  
15 fact that there are things the FDA can do and things  
16 the FDA can't do. These are the regulations. An act  
17 of Congress would change them, but it doesn't seem  
18 terribly likely. Let's work with this.

19 So within -- with that knowledge,  
20 supplement as we can. So I would like to think about  
21 creating working groups to create a credible way to  
22 work with the available data. We do need to talk

1 about the, in particular, talk about the idea of  
2 adequate and the words adequate and well. The patient  
3 with the word adequate, remember that patients and  
4 physicians will accept different tradeoffs. The word  
5 well, I'm not arguing about control, but what's the  
6 definition of well.

7 Remember that 100 patients equals \$10  
8 million more or less and several years' worth of work.  
9 It's not trivial data and it's hard to get all the  
10 information you want. Can we supplement with external  
11 controls? We're going to hear a talk today about  
12 sharing across -- same as yesterday, sharing across  
13 body sites. All of this stuff needs to get brought  
14 together to talk about what can we do inside the label  
15 to supplement the label, and at the same time, we need  
16 to do this. Agencies, societies and journals need to  
17 be spreading the words.

18 Superiority trials. I've already  
19 talked about that, and just last rant about  
20 superiority. Now, you have people who say if it's a  
21 superior trial, it would be so much smaller. Yeah,  
22 yeah, I know that, right? We all know that. But it's

1 not a path forward because we try to do those studies,  
2 it's lasagnas law. The patients go away because the  
3 hospital epidemiologists are making the resistant  
4 infection go away. And nobody wants to go to the  
5 hospital to test, there's a sign in front that says,  
6 world's leading center for resistant bacteria. Come  
7 and get your transplant, right? No, no, no, no, you  
8 don't want that at all. You want that to not be the  
9 case. And this is not a migraine. We're talking  
10 about a place where superiority means something bad  
11 happened.

12 This is the next message: non-  
13 inferiority is not a synonym for worthless, and  
14 guidelines need to be -- or guidances need to be  
15 continuously updated. And colistin, please, if I get  
16 sick, do not give me that poison; give me a real drug.

17  
18 Finally, industry needs to be aware of  
19 the constraints on the first previous three slides and  
20 to focus on novelty and unmet need. You know, Kevin  
21 talked yesterday about the need for incentives and  
22 different models and that's not today's discussion,



1 but there's a group of us working very hard on pull  
2 incentives. But I will tell you this: I think some of  
3 those are going to come to be, but they're not going  
4 to come to be for every drug.

5 If you're working in this area, it's  
6 your job to pick something that you think moves the  
7 needle. QIDP alone is not going to move the needle.  
8 You've got to actually be doing more than that.

9 So to close at this, you know, at  
10 heart, I'm an ID doc. I moved into industry in 2003  
11 because I spent -- a couple of things: antifungal  
12 pipelines were coming to a grinding halt, there was  
13 nothing to work on really; and I had spent five years  
14 as an epidemiologist, and I was starting to see  
15 infections at our hospital that can only be treated  
16 with (indiscernible).

17 I once closed an ICU for about a week  
18 because we had an outbreak of a then-untreated  
19 infection, and I shut down all the ORs. I said you  
20 can't do anything elective, you know, which made a lot  
21 of people unhappy. We stomped it out. It was an  
22 (indiscernible) bacteria outbreaks. You know, I'm

1 seriously hoping these nasty (indiscernible) will  
2 work. But that's the kind of thing that drives us all  
3 to be here.

4           Since then, I have walked all sides of  
5 this -- large pharma, small pharma, VC, philanthropic  
6 funders, you know, all that. And my deepest message  
7 is that tradeoff-free solutions to antimicrobial  
8 resistance do not exist; if they did, we'd all use  
9 them. Since they don't, we, as a community, it's the  
10 time for us to move forward with making the best  
11 available tradeoffs, preferably by 1:00 p.m. today.  
12 Okay? Thank you.

13           JANE KNISELY: Our next speaker is Dr.  
14 Vance Fowler. He's a Professor of Medicine at Duke  
15 University School of Medicine. His research interest  
16 focuses on staphoreious clinical epidemiology and  
17 pathogenesis. And he's led important clinical trials,  
18 testing new therapies for staphoreious bacteremia,  
19 including a randomized controlled trial comparing  
20 daptomycin to standard therapy. And I'm a little  
21 surprised that not in his bio, he is also one of the  
22 PIs of the Antibacterial Resistance Leadership Group.

1                   VANCE FOWLER: Thanks. These are my  
2 disclosures. I'm going to pick up on the point that  
3 John made that there are some things that the FDA can  
4 do and some things the FDA can't do. And I'm going to  
5 pick up from primarily from the perspective of the  
6 clinical need. Because the bottom line is, I feel  
7 like we in the scientific community are going to have  
8 to ultimately generate the data that we need to manage  
9 the patients that we see.

10                   My points of this talk are outlined  
11 here. Registrational trials necessary, not  
12 sufficient. Strategy trials, and I'm going to  
13 emphasize that hard because I honestly feel like  
14 that's giving the people what they want, and in  
15 clinical networks to help both approaches.

16                   So what do clinicians want? Well,  
17 they've told us what they want. This is a paper from  
18 2013 in which a large group of Australian ID  
19 physicians were asked what they actually need in  
20 clinical trials. And there are some pretty familiar  
21 faces here for those of you practicing, per se; joint  
22 infection, osteoarticular infection, uncomplicated

1 staphoreious bacteremia, diabetic foot infection, and  
2 treating ESDLs and then there were a variation on  
3 that.

4           And if you actually took these 13 top  
5 prioritized items and broke them down into four  
6 categories, they were fundamentally listed here:  
7 duration of ID antibiotics, how long do we treat these  
8 patients; combination drugs, are two drugs better than  
9 one; specifically, how do we treat MDR pathogens; and  
10 then root of administration, can we use PO antibiotics  
11 and abbreviate the time a patient has a line in.

12           These are the four categories, and I'm  
13 going to come back to this because this is going to be  
14 the benchmark against which I'm going to compare the  
15 registrational trials that have been employed and the  
16 strategy trials.

17           So in terms of registrational trials  
18 and agents that have been approved from 2013 to '18,  
19 and I'll limit my discussion to 2018, so there were  
20 the four agents. Again, this is through 2018 for skin  
21 and soft tissue, complicated UTI, intrabdominal  
22 infection; also acquired pneumonia, the

1 (indiscernible) from way back in the day, and the  
2 (indiscernible).

3 So if you look at the actual trials  
4 that were published, phase three registration trials  
5 published in 2018, there were basically five. There  
6 was the American and Vapor vacuum study, two ABSSSI  
7 studies for delafloxacin, and two ABSSSI studies for  
8 (indiscernible).

9 So I'll bring you back to that metric  
10 of the studies that ID clinicians actually want, none  
11 of which were addressed by the registrational trials  
12 from 2013 to 2018, so that's my point. And that's not  
13 being disrespectful to the FDA; these are just the  
14 facts. So now, and the problem brought this up  
15 yesterday -- Helen brought it up, I brought it up --  
16 you still have to make a decision. So these are three  
17 new drugs -- well, cefazoline's not quite so new  
18 anymore, but new enough -- taz-avi and  
19 (indiscernible).

20 So what I did was I went back for the  
21 first quarter of 2018 at Duke, and I asked the  
22 question, are these drugs being used, and, if so,

1 where are they being used. And the data shown here is  
2 they're about somewhere around 45 or 50 patients,  
3 unique patients, who have been treated; 87 percent  
4 were being treated off-label, so this is an N1 47  
5 times.

6 And this is the problem right here,  
7 it's an inconvenient truth, but here we are. Clinical  
8 trials don't equal clinical practice. Erythema not  
9 receiving in 72 hours alone; to me, that doesn't mean  
10 failure. Not obtaining a blood culture six weeks  
11 after stopping antibiotics for a patient with  
12 staphoreious bacteremia, guess what, that's not a  
13 failure. And if a patient gets four days of drug B  
14 after getting drug A, not a failure.

15 So what's the point then? The point  
16 is, you know, that we as clinical trialists and we as  
17 clinicians really are tasked with importantly  
18 different responsibilities, both of them essential,  
19 but really significantly different. And so, because  
20 of that, I'd like to argue that strategy trials really  
21 go a long way towards addressing the trials clinicians  
22 want.

1                   And I'll do that by demonstrating the  
2 strategy trials that were undertaken in 2018, so there  
3 were six of them. There was Stephen Harbath's paper  
4 on comparing nitrofurantoin for a single dose phosphor  
5 for uncomplicated UTI. Colistin monotherapy versus  
6 combination therapy for treatment of carbon resistant  
7 gram-negatives from Israel. The Danish POET study  
8 about using partial oral antibiotics for treatment of  
9 endocarditis. The ARREST study which tested the  
10 hypothesis that rifampin added to standard therapy  
11 improved outcomes in patients with staphoreious  
12 bacteremia. The comparison of piperacillin versus  
13 meropenem in the Marino trial. And the untesting of  
14 an algorithm versus standard care for staphylococcal  
15 bacteria. These were all published in 2018.

16                   And if you go back to the original grid  
17 that I showed about the metrics of what patients --  
18 what clinicians want and what they're provided, the  
19 registrational trials are shown there. All of those  
20 categories were addressed by strategy trials published  
21 in 2018. So there are differences in these things.  
22 We've alluded to it, but sort of to nail it down a bit

1 more refined, the purposes are different.

2 As I see the registrational trial, the  
3 primary objective is to make drugs available to  
4 practitioners and their patients. Strategy trials are  
5 primarily tasked with identifying the best means to  
6 use those drugs. The audience is different. At the  
7 end of the day, registrational trials, the audience of  
8 registrational trials are for regulatory agencies,  
9 with good reason.

10 By contrast, strategy trials are  
11 primarily tasked with an audience of the scientific  
12 community. The study design is different. I talked  
13 at length yesterday about the prototypical sort of  
14 ABSSSI and the complicated UTI designs and the reason  
15 that those well-established protocols are so  
16 important; test the drug, not the test.

17 Strategy trials, you're tasked with  
18 answering the clinical question. The consequences of  
19 failure are dramatically different. If you fail in a  
20 registrational trial, the compound is scrapped and the  
21 company may close. If you fail in your strategy  
22 trial, you publish in class one. The cost is



1 different and the complexity is different.

2           So what about networks, how do we fold  
3 this in, you know? And one of the challenges I think  
4 is U.S. site enrollment. Those were really nice  
5 presentations yesterday morning with some really clear  
6 data on the challenges of U.S. site enrollment. But  
7 it's interesting to remember, despite that fact, most  
8 clinical patients in clinical trials are enrolled from  
9 the U.S. -- this actually came from the FDA website  
10 and from a document from 2015 -- and it's not just a  
11 little, it's a lot. And that actually is not limited  
12 to other diseases, but is specific to infectious  
13 disease, as well, so that's point one. Most clinical  
14 patients in trials remain enrolling from the U.S.

15           The second point, though, is the U.S.  
16 site performance in ID clinical trials is variable.  
17 It really depends on what we're talking about and need  
18 to get into the details. So here's an example from  
19 complicated UTI -- these are data that were provided  
20 to me by a sponsor years ago -- with regards to the  
21 number of sites, the location of sites and the number  
22 of patients they enroll. This was for greater than a

1 thousand patients who were enrolled into two phase  
2 three identical design complicated UTI trials. Over  
3 96 percent of the patients were enrolled outside of  
4 the U.S.; out of the 1,060 odd patients, 23 were  
5 enrolled from the United States.

6 Now, let's compare that to another  
7 study. So this is an adjunct therapy for staphoreious  
8 bacteremia that I presented at ECCMID last spring.  
9 Over a hundred patients in the phase two; 80 percent  
10 of those patients were enrolled within the United  
11 States. So then the question is, you know, what makes  
12 a study enrollable in the United States?

13 These are some criteria that I've kind  
14 of put together that seems to make sense. First of  
15 all, the patient's got to be there, and the sort of  
16 case in point in that instance is the ABSSSI  
17 experience. We saw yesterday that ABSSSI was the one  
18 indication in which the U.S. continues to increase its  
19 numbers, and that's largely due to -- I would argue,  
20 largely due to a handful of investigators out in the  
21 Southwestern United States in the San Diego region.  
22 And by contrast, in the R pathogens, unless it's ESBR

1 or MRSA, I'm sorry, but we don't have enough numbers  
2 in the U.S. to conduct a U.S. limited trial in those  
3 pathogens. And that's a good thing, we want to keep  
4 it that way. It's got to integrate with clinical  
5 practice.

6           The reason these single dose adjuncts  
7 were primarily useful or enrollable in the U.S. had to  
8 do with the fact that it didn't delay discharge. By  
9 contract, a complicated UTI, even in the modified  
10 guidance now, more or less mandates if it's an IV  
11 drug, the patient's got to be in the hospital for five  
12 days. That's not going to happen in 2019 in most  
13 medical practices, not going to happen in the United  
14 States. They're going out, and you see that in the  
15 reality that the numbers bear out.

16           The patient need to own the disease.  
17 Somebody alluded to that yesterday in terms of  
18 HABP/VABP, and I couldn't agree more. You don't talk  
19 to the ID physicians if you want to -- if you're going  
20 after a HABP/VABP trial; you talk to folks like  
21 (indiscernible). You talk to intensivists because  
22 they're the ones who have access to the trial. Now,

1 let's compare that to a complicated UTI. Who owns  
2 that? The ambulatory care guy, the ER person, the ID  
3 guy, the urologist; where do you get them? You don't,  
4 and so we don't. The pathogens need to be there, and  
5 we talk about that. ESBL and MRSA, yes, maybe; MDR,  
6 not yet.

7 And then I think patient comorbidity  
8 needs to be reasonable limit. The VRE example is, I  
9 think, a case in point to that from, you know, a  
10 decade ago.

11 So some other obstacles to U.S. site-  
12 based research. And, you know, insufficient trial  
13 volume to maintain site infrastructure. You get a  
14 cool study. It's, like, wow, this is a really cool  
15 study. Where's the coordinator? Oh, you got to go  
16 hire a coordinator. Okay. And then I got to assume  
17 that I'm going to be enroll enough to be able to pay  
18 that coordinator just to break even so that the  
19 division chief doesn't come back, you know, banging on  
20 your head.

21 So second point: the site work is  
22 academically undervalued. There are a lot of

1 academics in the area, myself included. I know we've  
2 all written a lot of letters of promotion. Ask  
3 yourself this question: how many times have you ever  
4 written in your promotion letter, this person should  
5 be promoted to tenure because they were a great site  
6 enroller. Don't answer it out loud, but think about  
7 it and let me understand. And I think we all probably  
8 know the answer: bureaucracy, crushing bureaucracy.  
9 And it's both, it's with local and broader.

10 All right. So what are some partial --  
11 emphasis on partial -- solutions? I totally agree  
12 with John's point that this is a -- we're in a  
13 significant problem here and there's not going to be  
14 any single panacea. I think networks can help.  
15 Broadly speaking, networks really fall into three  
16 flavors: there's an observational type, and I'll use  
17 in the case in point, the International Collaboration  
18 of Endocarditis. This is one that's very near and  
19 dear to my heart but, unfortunately, is not relevant  
20 to today's discussion, so this is the closest I'm gong  
21 to get to talk about ICE today.

22 Registrational one, and I put the CTTI

1 initiative up here because I believe this is the first  
2 public or published forum in which John Rex and others  
3 were able to describe what I think was a really cool  
4 idea. And then strategy-based networks; I'm using RLG  
5 as an example. The targets are different:  
6 observational, describe the disease; registrational,  
7 new drugs; strategy, best management.

8 So in terms of the registrational  
9 trial, this is, again, this is the paper that John  
10 really led, along with Aaron and others, in terms of a  
11 vision for how to address the issue of getting new  
12 drugs to market. And I'm very pleased that it may  
13 have informed somewhat the RFP that Wellcome Trust put  
14 out, and I'm really looking forward to hearing more  
15 information about that from my colleague.

16 But suffice it to say, the concept  
17 would be these are a series of sites focused on a  
18 particular disease entity, the sort of three or four  
19 that get drugs to market, and that there would be  
20 ongoing enrollment with warm-based maintenance such  
21 that control patients can be enrolled during that time  
22 and you support your infrastructure.

1           The advantages to that is it gives you  
2 the right sites for the right trials and that it  
3 maintains a trial infrastructure. The disadvantage is  
4 critical mass, and then the sponsors may not use it.  
5 We're assuming that they will, but at least some of  
6 the meetings that I've attended in the past  
7 surprisingly, you know, at least gave me reason to  
8 suspect that they may not always use these networks.  
9 Strategies Trials Network, ARG is one example, there  
10 are others. So the purpose of this: design,  
11 implement, manage, clinical research in clinical  
12 practice.

13           The renewal is I hope will be starting  
14 in December. And the three emphasis areas are  
15 diagnostics, diagnostics, clinical trials, and  
16 relevant science. It's not exclusively focused upon  
17 interventional drug studies; and, in fact, I think  
18 diagnostics would be an important way to inform the  
19 practice as well. There's been -- you know, we've  
20 been productive in the last couple of years, and I'm  
21 incredibly proud of the efforts of our collective  
22 team.

1                   So in summary then, the strategy  
2                   registrational trial networks I see fundamental differ  
3                   in regards to different functions. Registration, make  
4                   new drugs, treatment; strategy, identify new  
5                   treatment, best treatment, different audiences,  
6                   registrational, FDA/EMA; strategy trials; the  
7                   scientific community, different costs and complexity,  
8                   so a lot of differences. But there's a similar need  
9                   for high quality sites both in the U.S. and abroad,  
10                  and I think that's probably an area where alignment  
11                  can occur.

12                  So I've sought to make the points that  
13                  registrational trials are necessary, non-sufficient  
14                  strategy trials, giving the people what they want, and  
15                  clinical networks to improve U.S. participation in  
16                  both, acknowledge funding. And happy to jump into  
17                  questions, and I've been grateful for the time to  
18                  speak today. Thank you.

19                  DAN RUBIN: Thank you. Our next  
20                  speaker is Pam Tenaerts. She's the Executive Director  
21                  at the Clinical Trials Transformation Initiative,  
22                  where she works closely with its executive committee



1 to develop and implement strategies to accomplish  
2 CTTI's mission.

3 PAM AENAERTS: Good morning, everyone.  
4 Happy to be here and thanks for inviting me. So  
5 today, I'll be talking about what you can do to  
6 enhance enrollment strategies. We heard a lot about  
7 enrollment being an issue and clinical trials have  
8 that specifically, and I'm here to represent the work  
9 of the groups that have worked on this. These are my  
10 disclaimers.

11 And so, just a little bit about CTTI.  
12 So we're a public/private partnership, co-founded by  
13 Duke University and the Food and Drug Administration,  
14 and we have a mission to develop a drug of optional  
15 practices that will increase quality and efficiency of  
16 clinical trials. We basically come up with  
17 recommendations on how to do clinical trials better,  
18 and that's what we've always done until 2012, and I'll  
19 explain a little bit more about that.

20 Importantly, we involve all the  
21 stakeholders, and we're a membership-driven  
22 organization. But we involve a lot more organizations

1 than just our members; it's whoever is needed for the  
2 activity that we're working on. We're evidence-based  
3 in that we use a large social science team to help us  
4 go from opinion, because by gosh, when you get a group  
5 together on whatever the topic is that they're  
6 passionate about, everybody on that group typically  
7 knows how to make it better. It's not necessarily  
8 evidence-based, so that's what we use our social  
9 science team. And we've been lucky enough to have  
10 impact in policy documents and things like that.

11 I wanted to highlight a little bit  
12 about some of the work we do. We split that up in six  
13 areas of focus: quality, talked a little bit about  
14 quality by design yesterday about there's resources  
15 there; patient engagement is also a big focus of CTTI,  
16 which you might have suspected based on my comments  
17 yesterday. And then we also help make sure that  
18 there's investigators and sites to do the work, even  
19 though as you move forward, there'll still always be  
20 sites, but that model might be changing a little bit  
21 as we go to site lists and things like that.

22 Mobile clinical trials really could

1 have fit into a novel clinical trial design, but  
2 that's just where we use mobile technologies. In our  
3 case, it was after consenting, so not to recruit, not  
4 to consent, but to capture end points. And then  
5 within all the clinical trial designs, you have the  
6 antibacterial drug development program; that really is  
7 the topic of discussion today. We also have a lot of  
8 recommendations on the use of single IRB. IRBs came  
9 up yesterday too as, you know, the variability in  
10 approval processes, getting different consents, things  
11 like that.

12 So this is our antibacterial drug  
13 development. So before this, I would have said CTTI  
14 does process improvement on clinical trials, and then,  
15 oh, and we also do antibacterial drug development.  
16 FDA asked us to work on this in 2012, and we developed  
17 a couple of projects. There's a lot of you in the  
18 room here that have helped on these projects, so I  
19 want to thank you for that. We could not do this  
20 without the people that help us, free most of the  
21 time, so we really appreciate it.

22 We did three big topics,

1 (indiscernible) HABP/VABP trials, and the reason we  
2 picked that one is the reason we're here today, and  
3 it's how difficult it is to do these trials. And if  
4 we tackle the hardest issues, maybe some of that work  
5 could then apply to the other trials as well.  
6 Pediatric trials and areas of unmet need.

7           So today, I'm going to talk about the  
8 HABP/VABP studies we did, but we also did work on  
9 streamlining protocol elements and data collections.  
10 But the overwhelming thought was it's all great that  
11 we can streamline our protocols; that'll help us  
12 nothing if we don't have patients in the trial. So  
13 that's why we went back to HABP/VABP studies and try  
14 to figure out how to do these better, which included  
15 two portions, a risk factor study and some formative  
16 research.

17           We would really, really, really, really  
18 like to do an early enrollment of clinical trial,  
19 which is where we test the methodology. And Vance is  
20 laughing because we've shopped this around to a lot of  
21 people, but we would really like to do this. Haven't  
22 been able to do it yet, but it seems really if you

1 want to be evidence-based, you need to have evidence  
2 on your methodology, and this would prove it for early  
3 enrollment.

4           So why did we talk about early consent,  
5 is because there's an early need to treat HABP/VABP;  
6 we've learned that today. There are few ongoing or  
7 planned HABP/VABP. But this must be cyclical because  
8 when we started in 2014, there were very few. When we  
9 came out with our work on early consent in 2017-'18,  
10 all of a sudden, there were a couple, and we were,  
11 like, oh, we don't want to compete for patients that  
12 should go into real treatment trials with our  
13 methodology trials, so we put it on hold a little bit.  
14 And then now, there's like there's no -- almost no  
15 HABP/VABP trials again.

16           So anyway, so what we talked about is -  
17 - and I have that project. And the other thing is,  
18 you know, we all know that enrollment rates are, you  
19 know, abysmal, they're really low, and the cost of  
20 enrolling a patient is really high. We also did work  
21 with Tufts University on the cost of trials, patients  
22 in HABP/VABP trials and it's about \$100,000 per

1 patient, this is not trivial, and this is for a  
2 patient enrolled.

3           So we looked at that and we had a lot  
4 of discussions about this. And at one of the  
5 meetings, the patient said, well, why don't you ask me  
6 to be part of an HABP/VABP study when I'm still there,  
7 when I still can consent, and we tossed that around.  
8 But Vance really turned it into something that was  
9 manageable where we could figure out risk factors.  
10 Because if you want to consent a lot of people up  
11 front, you probably don't want to consent a hundred to  
12 get one patient that ends up with a pneumonia, but  
13 something reasonable that somebody could pay for as  
14 far as creating consenting and that. And so, we  
15 needed to figure out how to get there.

16           So we wanted to do this before they're  
17 critically ill because we hope that the patient, the  
18 participant could actually participate in the  
19 discussion. The family could be there. So by the  
20 time the patient down the road has HABP/VABP, is  
21 potentially on a ventilator, nobody has to sort of  
22 worry, like, would grandpa really want to do this or

1 not. You kind of know because you were part of the  
2 discussion.

3           And we then figured out how to actually  
4 do this. So we did ask to do a demonstration study;  
5 we haven't been able to do that. So the reason we  
6 went to early consent is in our streamlining HABP/VABP  
7 work, we did a lot of project team discussions and  
8 focus groups who'd experienced court leaders, and it  
9 really was a challenge to enrolling. The 24-hour  
10 timeline is the big bugaboo here. And we sort of  
11 appealed, like, well, can't we make that 48 hours; for  
12 a while we were on the track of let's extend it out to  
13 48. And there's been scientific reasons why you  
14 shouldn't be doing that, so the 24 really is sort of  
15 something. But then this early enrollment could  
16 really help with that.

17           So even when the patients -- you know,  
18 this is prior to effective antibiotic therapy. So if  
19 the patient is identified before 24 hours, it's  
20 difficult to conduct all these things that you need to  
21 do -- consent, labs, study, drug availability -- in  
22 that 24 hours. So how can you do this by beginning

1 consent before the HABP/VABP develops? So you would  
2 approach and consent patients at high risk before the  
3 24 hours, before the antibiotics are started, and  
4 before the symptoms develop.

5           So you would do all that ahead of time,  
6 and then you would enroll the patient the minute they  
7 would actually develop the diagnosis of -- when you  
8 would normally start your planned antibiotics. This  
9 is where now, if you had consented early, this is  
10 where you can now start them in the study instead of  
11 starting them on the regular antibiotics that you  
12 would normally starting them.

13           And, like I said, we had planned to  
14 conduct a study, which we have not done. If anybody  
15 wants to talk about that, I'll be here until 1:00.

16           So if you want to think about doing  
17 this, you have to first find the patients that you  
18 would want to consent early, and then figure out  
19 whether this is even acceptable or feasible. Because  
20 when this plan started coming together, there were a  
21 lot of people that said, oh, the IRBs are never going  
22 to go for this; we heard that from a lot of people.



1           So we wanted to do both: can we find a  
2 set of patients that you could consent that makes  
3 economic sense for a sponsor to pay for those  
4 consenting and screening procedures; and then, how do  
5 you get that done, like, how do you make that  
6 acceptable and feasible both for the participants, the  
7 science, and the IRBs.

8           So we did some preliminary research;  
9 it's really determining the population that you should  
10 approach early. And after a lot of planning, we sort  
11 of came up with following the oxygen in the ICU,  
12 because we figure that running -- there's plenty of  
13 patients that develop pneumonia outside of the ICU,  
14 we're very well aware of that. But, I mean,  
15 logistically, that's just not an easy thing to start,  
16 you know, go after. The ICU is contained, so we  
17 figured if we could find a population there, that  
18 would make sense for the coordinator to do that.

19           So we identified, we did a risk factor  
20 study in the U.S.; the EU participated with a comeback  
21 network. And I heard somebody talk about they were  
22 participating on our studies as well. And then we

1 also did pediatric sites because they also have that  
2 issue.

3           So we looked at -- we required invasive  
4 or non-invasive ventilation, so this following the  
5 oxygen idea, and you had to be receiving antibiotics  
6 for suspected pneumonia. So in total, we enrolled  
7 7500 patients. This is -- I'm going to talk a little  
8 bit more about the U.S. one because we're a little  
9 further along. Europe took a little longer, and then  
10 the pediatrics people are working on their section.

11           So this study in the U.S. lasted about  
12 eight months in 2016, so this is a pretty short  
13 enrollment period. And we identified patients that  
14 were high risk, so they had to receive more than 12  
15 hours of treatment with invasive and non-invasive  
16 mechanical ventilation or high levels of oxygen within  
17 the past seven days. And of the 7500, 4632 were high  
18 risk, identified as high risk; 1400 -- so 1500  
19 patients were actually treated for pneumonia; and of  
20 those, 539 met the FDA guidance criteria for  
21 HABP/VABP.

22           So let that sink in a little bit. How

1 many of you have gotten, you know, those cards about  
2 my hospital has not had any hospital-acquired  
3 infections? So this kind of shows that HABP/VABP is  
4 alive and well, so this is another thing to think  
5 about. But what we basically found is, you can  
6 identify patients that basically if you'd consented  
7 10, one of them would have pneumonia.

8           So like I said, we could quasi-predict  
9 who might get pneumonia, but you could enrich that  
10 sample with other things based on the ICU admission,  
11 what had they received. So you can enrich that sample  
12 and make it a little richer; documented aspiration  
13 risk, admissions source have received of systematic,  
14 and the bacterial in the last 90 days were additional  
15 risk factors. So if you combine that, you could  
16 really identify prospectively patients for an early  
17 enrollment strategy.

18           So, okay, that part is done. We can  
19 find the patients reasonably that a coordinator could  
20 work with to see if they were to develop pneumonia.

21           How about the other thing; is this  
22 acceptable and feasible? What concerns would an IRB

1 have about this early enrollment strategy? How  
2 burdensome would it be to the trial investigators and  
3 the study coordinators, because you don't want to make  
4 it a whole lot harder. And how would patients and  
5 caregivers feel about enrolling in a clinical trial,  
6 and they don't even have the condition for what's  
7 going to happen. Not only will they not have the  
8 condition, but they're pretty sick already.

9           So here is somebody who is really sick  
10 coming into an ICU and somebody's going to come to  
11 talk to them about, oh, and by the way, not only do  
12 you have everything you have, we think you're at high  
13 risk for pneumonia. So this is something that people  
14 thought may not go over very well. And if we did  
15 that, what would patients want to know about this  
16 approach so they can make an informed decision and not  
17 sort of a screaming and run away, so we did formative  
18 research.

19           So we did in-depth interviews, and then  
20 those people were then also asked to participate in  
21 two surveys. The interviews dealt with the  
22 acceptability and preferences for components of that

1 strategy and kind of figuring out what topics we  
2 should describe in the early consent. And then with  
3 our online survey, we delved deeper into that into  
4 really getting at the sentences we should be using.  
5 And then the last survey was final agreement of the  
6 language to include in the consent.

7 And the people that participated in  
8 this research, in this formative research were  
9 patients, caregivers, investigators, study  
10 coordinators, and IRBs, so we kind of tried to get  
11 everybody that might have an opinion on this.

12 So what the patients and legal  
13 representatives thought is that this is really not  
14 that hard. I mean, they could accept this very  
15 readily; that early consent and enrollment strategy  
16 was overwhelmingly accepted. They found it acceptable  
17 that their charts would be monitored, because that  
18 would come with that obviously before the acquired the  
19 pneumonia; they could understand the consent  
20 information before the -- you know, before they would  
21 be diagnosed with HABP/VABP, in this case, and they  
22 would be willing participated under early enrollment

1 trial using approved antibiotics. They felt a little  
2 more iffy about the newly ones, but, I mean, we could  
3 probably get there, but some others don't work.

4           When we asked investigators and IRB,  
5 they kind of felt that this early enrollment strategy,  
6 you know, may work. The investigators thought, like,  
7 oh, this could maybe work. And it may improve  
8 efficiency of the trial conduct for HABP/VABP. And we  
9 hope to think that this also shows that we might  
10 potentially be able to do this in other conditions  
11 where, you know, there's sort of acute things that  
12 happen in a chronic patient.

13           None of the IRB members raised concerns  
14 about the early enrollment strategy. So, honestly,  
15 they said this sounds pretty straightforward, it  
16 doesn't sound like it's going to cause a great deal of  
17 concern. And, you know, there would have to be a  
18 discussion about the possibility, the percentages, the  
19 chances that might happen, but not looking at this as  
20 something unusually concerning.

21           What needs to be in that consent ahead  
22 of time? So they would want to rationale for the

1 early enrollment strategy; they would have to have  
2 explanations about non-inferiority. As you can  
3 imagine, this was not the easiest concept for anyone  
4 to understand. And so this was something that you  
5 could actually take your time with and close the  
6 patient or the perspective participant potentially.  
7 And their family were there, so this is not like, you  
8 know, your family member is on a ventilator and you're  
9 freaking out a little bit.

10           Reassurances as to what would happen if  
11 the studied drug might not be working. We asked them  
12 how they would explain that information, and then we  
13 used that information to develop and obtain agreement  
14 on the text that should be used in the consent, and we  
15 have finalized texts for all of the issues that they  
16 mentioned in the consent.

17           This is available in a publication, and  
18 the survey data and the final consent is also going to  
19 be published later this year. This got caught up a  
20 little bit and, you know, we talked yesterday about  
21 pre-prints a little bit. And we've starting doing  
22 pre-print articles because feel that it takes too long

1 to publish, and we are not the hot topic in many  
2 cases. You know, we've tried to, you know, go to ID,  
3 you know, all these -- we just find it hard -- it's  
4 hard to publish these things. We finally found a  
5 place, but we're going to go more to pre-print. We  
6 haven't done it with this project yet, but if we had,  
7 it would be available already.

8 We also think that you could use this  
9 in other diseases and applications and, you know,  
10 other ICU acquired infections or infections that tend  
11 to occur, UTIs, (indiscernible), you know, sepsis,  
12 other chronic conditions with frequent exasperations  
13 like I mentioned earlier, or conditions in which  
14 patients have periods of decisional incapacity where  
15 for times, they can't make decision maybe so you can  
16 talk about this ahead of time.

17 I would say, though, that when we  
18 talked to patients and IRBs about this, while they  
19 happily wanted to consent ahead of time, they would  
20 like a little heads up when it actually would start.  
21 Like, it wouldn't be -- you know, you wouldn't know  
22 when you were getting into the research study. So



1 there would be some type of, you know, hey, you  
2 remember what we talked about; we're going to start  
3 and this is the specific study we're going to put you  
4 in.

5           So this may improve efficiency of  
6 clinical trial conduct for HABP/VABP, and it was  
7 overwhelmingly accepted. Prospectively identifying  
8 these patients requires high level of following the  
9 oxygen basically, and you could enrich it. And we are  
10 developing tools to assist with this trial planning;  
11 we're going to come out with the consent language.  
12 We'll publicly share the risk factor data.

13           We're actually going to put all that  
14 clinical data online with levers that if you want to  
15 look at your inclusion/exclusion criteria, you could  
16 sort of move them around on whatever the topic is  
17 you're measuring to kind of see that in our  
18 population, how that would have affected enrollment,  
19 whether you would exclude patients or not. And we're  
20 also creating a trial planning -- that's the trial  
21 planning tool I talked about, and that's it. Thank  
22 you.

1 JANE KNISELY: Our next speaker is  
2 Chibuzor Uchea, a Senior Officer in Wellcome Trust  
3 Drug-Resistant Infection Priority Program, working on  
4 a range of projects focused on the development of new  
5 treatments and diagnostics and improving the  
6 efficiency of clinical trials. He joined Wellcome in  
7 June of 2019 after three years of working in  
8 healthcare consultancy.

9 CHIBUZOR UCHEA: Good morning,  
10 everybody. Thank you for the introduction. I'd like  
11 to also thank the organizers for inviting me here to  
12 speak. It's a pleasure to be here.

13 So as was mentioned, I'm from the  
14 Wellcome Trust. And for those of you who are familiar  
15 with us, we're a charitable foundation that supports  
16 research to improve health around the world. We have  
17 a mission of taking on eight global health challenges,  
18 making an impact by meeting the response through our  
19 priority program.

20 The drug-resistant infections program  
21 is one of these, and it aims to use Wellcome's  
22 funding, convening, advocacy, and influencing power to

1 help lead the global response to antimicrobial  
2 resistance. Our program has a strategy that's based  
3 on four pillars, which represent key areas of unmet  
4 need, but also opportunities in which Wellcome are  
5 well placed to be able to make an impact.

6 The four pillars of this strategy can  
7 be seen here. I would like to call your attention to  
8 the two on the right-hand side, which are most  
9 relevant to this workshop: that's the development of  
10 new therapeutics, and the acceleration of clinical  
11 trials.

12 We have a vision of developing a  
13 pipeline that's sustainable to develop antibiotics,  
14 diagnostics, and vaccines for infectious diseases to  
15 protect local public health. This is reflected by our  
16 commitment to CARB-X. As Aaron mentioned yesterday,  
17 we're a funder and it remains our greatest investment  
18 of \$155 million across five years.

19 And also our work with the  
20 (indiscernible) program in collaboration with the  
21 Innovative Medicines Institute. As the pipeline  
22 strengthens, clinical development will become an even

1 tighter bottleneck, and we're committed to developing  
2 initiatives that will help accelerate (indiscernible).

3 We also have a strong policy and  
4 advocacy focus, and we interact with key decision  
5 makers in all of our activities as we recognize that  
6 antimicrobial resistance has an urgent need for global  
7 action.

8 So the current funding model of  
9 clinical development in infectious diseases is complex  
10 and burdened with a range of inefficiencies that slow  
11 down the commercialization of antibiotics. This is  
12 especially true in low- and middle-income countries,  
13 and is reflected by the disparity between the number  
14 of trials that were run in these countries and the  
15 burden of antimicrobial resistance.

16 A key driver of this is the ad hoc  
17 funding nature of individual trials, whereas sponsors  
18 custom build a single use network of trial sites,  
19 spending considerable amounts of money building  
20 capacity and infrastructure and training staff on  
21 individual protocols. At the end of these trials, the  
22 capacity is disbanded, and there's a loss of

1 infrastructure and expertise within sites as well.  
2 Subsequent funders then come in and spend considerable  
3 amounts of money reactivating sites, redeveloping  
4 infrastructure, and training new members of staff on  
5 subsequent protocols.

6 Another key issue, as mentioned  
7 yesterday, are issues with patients recruitment. And  
8 because of the clinical nature of infectious diseases,  
9 there's a very narrow window for recruitment. And  
10 also, as described yesterday, it's not only impossible  
11 to be able to move patients to various different  
12 sites.

13 Also, if the focus on studies in high  
14 income countries, there's difficulty in finding  
15 patients with -- some of them more difficult to treat  
16 infections, especially if they're multi-drug resistant  
17 and extensively drug-resistant indications. Whereas,  
18 there were a much wider pool of patients in low- and  
19 middle-income countries with these extensive drug-  
20 resistant infections because of the increased burden  
21 of antimicrobial resistance.

22 And in low- and middle-income

1 countries, there were also issues with the  
2 (indiscernible) of trial site quality, which affects  
3 the quality of the data that it produced, and also the  
4 requirement for individual studies for each indication  
5 exacerbates the issues with our funding model.

6 So what are the proposed solutions for  
7 these problems? We have a vision of accelerating  
8 clinical development in this space using a two-pronged  
9 approach that will address the various different  
10 barriers.

11 The first of these is the development  
12 of international clinical trial networks, which will  
13 strengthen the clinical trial capabilities within low-  
14 and middle-income countries, alleviating the  
15 inefficiencies of the current ad hoc funding model and  
16 vitally provide access to large populations of  
17 patients with key drug-resistant infections.

18 We have a vision of these networks  
19 being able to run multiple studies from different  
20 funders simultaneously.

21 Our second approach is the development  
22 of platforms for innovative trial design, especially

1 the use of continuous master protocols. This will  
2 allow control group sharing between trials and reduce  
3 costs and burdens.

4           These two aspects are independent, but  
5 also complementary, and joint implementation will  
6 provide even greater efficiencies.

7           So the first of these is the  
8 international clinical trial networks. And we're  
9 working towards developing a pilot network that's  
10 going to be entered in Southeast Asia. It will start  
11 as a flexible scalable regional network of high-  
12 quality sites, which it will be building on existing  
13 capacity, and vitally will provide rapid access to the  
14 Southeast Asian population with a high burden of  
15 antimicrobial resistance.

16           Our model will be (indiscernible) with  
17 other regional networks, which will be vital for us to  
18 be able to broaden our base, and also will provide  
19 access to key expertise in infectious diseases  
20 internationally. Another key aspect of this is that  
21 we would be able to leverage key learnings from the  
22 development of other clinical trial networks.

1           Our business model will be orientated  
2 to be able to engage with the private sector, which  
3 will allow us the support by investigating initiated  
4 studies and registrational studies. We've identified  
5 our nucleus of sites who will be our founding members,  
6 and we aim to launch the network around an initial  
7 trial, which will be used to test and help develop the  
8 network and also inform scale.

9           An effective clinical trial network  
10 will provide a range of benefits to a number of  
11 stakeholders, including sponsors, investigators, and  
12 ultimately patients. For sponsors, there will be  
13 reduced costs of conducting trials through warm-based  
14 benefits, and also will facilitate power around follow  
15 on studies and optimization studies for strategy  
16 trials as (indiscernible)'s ability.

17           For investigators, crucially will  
18 provide access to keep populations with high burden of  
19 disease, and also will improve the quality of trial  
20 sites in the region, improving the data that are  
21 produced and helping to produce better studies.

22           And ultimately for patients, it will



1 increase the speed at which treatments have become  
2 available, and also potentially make them cheaper  
3 through reduced developmental costs.

4 We've recently commissioned a piece of  
5 work, which is looking at how best to structure the  
6 network to maximize our possibilities of success. And  
7 the process we engaged in with a range of stakeholders  
8 from industry, clinical trial experts, as well as  
9 other members from other clinical trial networks.

10 Our own grading model will be with the  
11 network secretariat, which is responsible for managing  
12 and coordinating central functions, and also it will  
13 be guided by a steering committee which will provide  
14 strategic oversight. The responsibilities and roles  
15 of the secretariat include pipeline management and  
16 regulatory engagement and market access, which will be  
17 vital for the long-term sustainability of the network,  
18 as well as administrative functions.

19 We've also identified key areas which  
20 are vital for startup, and also others which are more  
21 important for the long-term vision of the network.  
22 These include geography; we've identified our founding

1 members, but we are also looking to expand, and we can  
2 add additional sites that match the site quality  
3 criteria to the network. We're currently engaged in  
4 conversations with sites and institutions in India,  
5 which will further increase our geography and vitally  
6 access to either ratable patients.

7           The network will start by looking at,  
8 investigate and initiate treatment trials within drug-  
9 resistant infections, but we'll scale up to include  
10 studies from sponsors in a commercial sector and also  
11 looking at infectious diseases in general.

12           We're currently working to finalize our  
13 governance structure, which will be ready at the end  
14 of the year, and then we will start to recruit for our  
15 secretariat function, as well as identifying and  
16 developing the initial clinical trial, which will be  
17 across next year.

18           There are a number of potential  
19 challenges of developing international clinical trial  
20 networks, and these include a strong and robust and  
21 transparent governance structure, as well as alignment  
22 on direction within the network.

1 Another key aspect is potential for  
2 underuse of the network between studies. This is why  
3 to prevent a lot of times sustainability of the  
4 network. And the work we've commissioned has looked  
5 at the pipeline. And although there are considerable  
6 studies that can come into the network, there's also  
7 the opportunity in which there will be down time  
8 during -- when registrational studies are not  
9 available. For this reason, we will work for our  
10 network to be able to have the capacity and the  
11 expertise to run additional studies, especially more  
12 complicated studies, including pediatric studies and  
13 smaller optimization studies.

14 We're currently working to build out  
15 our secretariat function, which will provide support  
16 for the network to be able to address these  
17 challenges.

18 So the second approach is the use of  
19 innovative trial design. In 2016, we held a workshop  
20 assessing the benefits or potential benefits of using  
21 clinical trial networks for antibiotic development,  
22 which a number of you would have attended. An

1 innovative trial design through the use of continuous  
2 master protocols was highlighted as a key tool that  
3 could further accelerate the efficiencies that are  
4 provided through clinical trials, and a recommendation  
5 was made that this should be further explored.

6           Since then, we've commissioned some  
7 work to assess the feasibility of using continuous  
8 master protocols within clinical trial networks. And  
9 in the process, we engaged with key stakeholders in  
10 the industry, regulatory bodies, and John Rex has also  
11 been a great guide in our thinking. The continuous  
12 master protocol will provide even greater efficiencies  
13 by allowing the sharing of control groups within  
14 clinical trials with the same indications, which will  
15 reduce the enrollment periods and reduce the costs as  
16 well.

17           There's the possibility to use  
18 concurrent control groups within the same time periods  
19 have also potentially non-concurrent controls and  
20 possibly control data, historic control data from  
21 previous trials. And the use of adaptive  
22 randomization allows the flexibility of entering and

1 exit of compounds throughout the process, mitigating  
2 the irregular startup of regulatory studies.

3 Our feasibility assessment has shown  
4 that such a platform would be especially beneficial  
5 for undertaking regulatory science studies and later,  
6 expansion studies. We have identified sufficient  
7 demand for this among the stakeholders which we've  
8 engaged with.

9 The use of concurrent controls has been  
10 supported in principal by regulators. However, there  
11 remains considerable concerns and issues around the  
12 use of long concurrent controls as we discussed  
13 yesterday.

14 We have identified adult HAP/VAP and  
15 CAP studies, as well as pediatric studies as those  
16 that will benefit most from the use of the continuous  
17 master protocol, and we're currently exploring with  
18 other funders whether this type of platform is  
19 investible.

20 So in conclusion, we believe that the  
21 reason strengthening of the pipeline really demands a  
22 more efficient clinical development process. And the

1 initiatives that we've mentioned here today around the  
2 use of clinical trial networks and continuous master  
3 protocols will provide initiatives -- will provide  
4 additional benefits from a scientific, financial, and  
5 developmental perspective.

6           Importantly, conducting these in low-  
7 and middle-income countries will provide access to key  
8 populations of patients with drug-resistant  
9 infections.

10           DAN RUBIN: Thank you very much for the  
11 introduction. I'll try to keep my remarks brief to  
12 leave time for other speakers and for Q&A and to keep  
13 us on schedule.

14           One thing I might say is that after  
15 this stat session, we have some Q&A scheduled for all  
16 those talks. We didn't have any on the agenda for Q&A  
17 for the talks we just heard this morning. But maybe  
18 after all the stat speakers, we can have a Q&A for  
19 everything so far today and then go into the panel  
20 discussion later this afternoon.

21           What I'd like to do is provide some  
22 high-level comments about three important statistical

1 issues in anti-infective registration trials, which I  
2 hope will frame the discussion for this session.  
3 These issues are endpoints, borrowing information  
4 across body sites, and considerations for carbapenem-  
5 resistant pathogen studies.

6 With respect to endpoints, anti-  
7 infective registration trials have most commonly used  
8 binary endpoints in which each outcome is classified  
9 as a success or failure. The definitions recommended  
10 in our guidance document vary across the disease  
11 types. And hospital-acquired and ventilator-  
12 associated bacterial pneumonia, the main endpoint  
13 recommended in the guidance is all-cause mortality at  
14 a fixed time point following randomization between day  
15 14 and day 28. In trials of intra-abdominal  
16 infections, failure is based on a clinical  
17 determination of failure. And in complicated urinary  
18 tract infections, the primary endpoint is a composite  
19 based on both clinical and microbiological components.

20 Professor Evans will describe in more  
21 detail how binary endpoints could potentially be  
22 improved by moving to endpoints with finer gradations

1 of success and failure. For instance, one could  
2 consider an ordinal endpoint with the three levels of  
3 death, survival with major morbidity, and survival  
4 without major morbidity. The main advantage is that  
5 this may lead to more informative comparisons when  
6 reasons for failure are not all lumped together. And  
7 another advantage of this approach is that it can  
8 increase statistical power because it's making use of  
9 more information.

10 One consideration is that levels should  
11 be chosen so that differences will not be solely  
12 driven by effects on components with minor importance  
13 or solely by safety.

14 As a hypothetical example, if you  
15 wanted to show that a new drug was superior to say  
16 colistin and included reversible renal toxicity in an  
17 ordinal outcome, one thing to check would be whether a  
18 new drug could be superior to colistin using this type  
19 of outcome scale even if it was say increasing  
20 mortality. And this issue can be addressed to some  
21 extent by assigning weights or utilities to different  
22 categories.



1                   My understanding is that these forms of  
2 DOOR and RADAR methods have been used by ARLG, have  
3 mainly been proposed and implemented for superiority  
4 trials.

5                   Dr. Lewis will discuss borrowing  
6 information across body sites of infection. Some  
7 statistical methods such as Bayesian hierarchical  
8 models have been widely used for combining information  
9 from different sources, both in clinical trials and  
10 many other types of applications, but largely not in  
11 the anti-infective space.

12                   The models would attempt to provide an  
13 integrated or synthesized analysis of patients with  
14 different infection types.

15                   One way to think about information  
16 borrowing is that it tries to reduce noise for  
17 estimating treatment effects in any one body site by  
18 bringing in other relevant data. So for instance,  
19 suppose you have a very small number of patients with  
20 complicated intra-abdominal infections so that the  
21 estimated treatment effect will have a lot of  
22 variability. If there's a larger number of patients

1 with complicated urinary tract infections who have  
2 been treated with the same drug, then incorporating  
3 them into the analysis could in theory reduce this  
4 variability.

5           Of course the issue with doing this is  
6 that there is a reliance on modeling assumptions about  
7 the degree of similarity between infection types. So  
8 for estimating treatment effects in cIAI, you would no  
9 longer have the protection of a fully unbiased,  
10 randomized comparison.

11           One remark to point out is that FDA has  
12 at least informally used some forms of information  
13 borrowing in assessing anti-infective drugs even  
14 without use the full Bayesian machinery. For  
15 instance, an NDA can be based on a single successful  
16 Phase 3 trial for patients at one body site with  
17 supportive evidence from a related disease.

18           Registration trials do combining  
19 heterogenous patients, such as studies of both  
20 hospital-acquired and ventilator-associated bacterial  
21 pneumonia. And our unmet need guidance also accepts  
22 pooling body sites for superiority trials, and

1 registration trials in resistant pathogen studies have  
2 combined nosocomial pneumonia and bloodstream  
3 infections.

4 There are a few issues that FDA is  
5 likely to take into account when reviewing proposals  
6 for an integrated analysis of body sites. One issue  
7 would be statistical operating characteristics if  
8 treatment effects differ.

9 For instance, if there is a proposal to  
10 combine HABP/VABP, cIAI, and cUTI, and in truth the  
11 drug doesn't work in HABP/VABP, how inflated is the  
12 chance that the design will lead to a false conclusion  
13 of efficacy in HABP/VABP?

14 We may also consider previous history  
15 of discordant results of cross-body sites, such as  
16 with daptomycin not working well in pneumonia due to  
17 inactivation by pulmonary surfactant. And for  
18 deciding which data to integrate, this wouldn't just  
19 be a statistical decision; there would of course also  
20 need to be a clinical judgement that the infection  
21 types, pathogens, and endpoints make sense to combine  
22 in an integrated analysis.

1                   The last topic I'll touch upon are  
2 carbapenem-resistant pathogen studies, which are  
3 related to Dr. Dane's upcoming presentation. These  
4 studies are commendable because they do directly  
5 address questions most closely related to unmet  
6 medical needs.

7                   The main challenge is that enrollment  
8 in randomized trials has been very difficult, as you  
9 have heard over the course of the workshop, due in  
10 part to the rarity of the pathogens.

11                   I will just briefly note that there are  
12 some government or academic randomized trials that  
13 have compared combination therapy to colistin  
14 monotherapy in patients with carbapenem-resistant  
15 *Acinetobacter baumannii* infections, which have had some  
16 degree of success with enrollment and together have  
17 enrolled about 650 patients. And that's not including  
18 the OVERCOME study we heard about yesterday from Dr.  
19 Dixon. But I've referenced a metanalysis on this  
20 second bullet.

21                   If moving beyond randomized comparisons  
22 to external controls or non-randomized comparisons,

1 the key challenge is being able to control for  
2 confounding in patient populations with many comorbid  
3 conditions. Dr. Dan will go into more details about  
4 some of these considerations surrounding randomized  
5 and non-randomized evidence.

6 Our unmet need guidance also discusses  
7 pathways that have now been used by several sponsors  
8 based on another type of information borrowing. And  
9 this is where a non-inferiority trial is conducted in  
10 patients with susceptible pathogens, potentially with  
11 a wider than normal noninferiority margin. The  
12 labeling is then for patients with more limited  
13 treatment options with the constraints of the data  
14 package communicated in the labeling.

15 The main uncertainty of this approach  
16 relates to differences between patients with  
17 susceptible pathogens and the less well-characterized  
18 group with limited treatment options.

19 One question to consider about this  
20 form of extrapolation is whether the discordant  
21 directionality of numerical results in the carbapenem-  
22 resistant CARE trial of plazomicin and the CREDIBLE-CR

1 study of cefiderocol could have been predicted or  
2 explained based on all the preclinical information or  
3 from the successful non-inferiority trials conducted  
4 for each drug in carbapenem susceptible complicated  
5 UTI.

6 The caveat is that the numerical  
7 results in these two trials of carbapenem-resistant  
8 infections had statistical noise from the sample  
9 sizes. But the references in this bullet are to our  
10 advisory committee materials if you'd like to think  
11 more about this question.

12 The last point I'll make about  
13 carbapenem-resistant pathogen studies is that folding  
14 these patients into standard noninferiority trials but  
15 with more flexibility in the active comparator would  
16 follow the template used for previous types of  
17 resistance.

18 For instance, if evaluating a gram-  
19 positive drug, there wouldn't be a separate trial for  
20 MRSA. Patients with MRSA instead would most likely  
21 simply be included in a noninferiority trial of skin  
22 infections or pneumonia or bacteremia and there would

1 be provisions for patients in the control group to  
2 receive an agent with activity against MRSA.

3           The uncertainty or one of the main  
4 uncertainties that I see with using this approach for  
5 carbapenem-resistant infections is that any recently-  
6 approved active comparator might itself have been  
7 studied using relatively streamlined data. And this  
8 could limit the interpretability of noninferiority  
9 conclusions if there were remaining unanswered  
10 questions about the active control. And one term that  
11 has been used for this type of risk is biocreep.

12           Here are references for several of the  
13 topics that I've mentioned, and thank you.

14           JANE KNISELY: Thanks. Our next  
15 speaker is Dr. Roger Lewis. He is a Professor and  
16 Chair of the Department of Emergency Medicine at  
17 Harbor-UCLA and a Senior Medical Scientist at Berry  
18 Consultants. And he will be speaking about Bayesian  
19 adaptive clinical trials.

20           ROGER LEWIS: Great. Thank you very  
21 much. It's a pleasure to be here. Thank you to the  
22 organizers and the audience.

1           So I'm going to be talking about  
2           statistical approaches for antibiotic trials and  
3           posing the question, are we answering the wrong  
4           questions? But in posing that question, I hope to  
5           follow Dr. Rex's recommendation to actually give an  
6           alternative.

7           These are my disclosures.

8           So the take-home points are that the  
9           statistical and overall design strategies that are  
10          commonly used for antibiotic trials really should  
11          directly inform the clinical uses of products if they  
12          are approved. In light of how antimicrobials are  
13          actually used, I believe they should support  
14          antibiotic stewardship to the degree available or  
15          accessible within the regulations, and also inform  
16          regulatory approvals and labeling.

17          I put these points in this order  
18          because I believe that if you have trials that  
19          directly address the appropriate clinical use of an  
20          agent, that will naturally inform regulatory decision-  
21          making. But I believe as currently deigned, many  
22          trials in antibiotics do not meet these goals. They



1 are overly-narrowly focused. We heard amazing ratios  
2 of screen-to-enrollment numbers yesterday. They may  
3 predictably undermine some stewardship efforts, and  
4 they risk missing important benefits due to delayed  
5 initiation of agents and contamination of patients  
6 'outcomes by prior treatment, but they could address  
7 the goals.

8 So let's briefly go through an anatomy  
9 of an antibiotic trial as sometimes carried out. And  
10 I hope that I don't step on anybody's toes this way.

11 The patient presents commonly to an  
12 emergency department, which is where I work  
13 clinically. They have signs and symptoms of a serious  
14 bacterial infection. They are hopefully briefly  
15 evaluated, and empiric antibiotic therapy is started  
16 very early because there is an important clinical and  
17 compliance imperative to do so. There is a small loss  
18 of patients if it's determined that treating the  
19 disease is not in the patient's interest and  
20 consistent with goals of care.

21 Some time after that, they are admitted  
22 to the hospital. And it's commonly in the in-hospital

1 setting in which they are first evaluated for an  
2 antibiotic trial. At some point it's confirmed that  
3 the intended single site of infection for the trial is  
4 in fact the infected site. Culture results come back  
5 that meet the criteria. At some point they're  
6 actually randomized. And if they are successfully  
7 enrolled and randomized, the investigational medical  
8 product is begun, and at some point there's an outcome  
9 assessment.

10                   There's a long period of time where  
11 they are receiving empiric therapy prior to  
12 randomization, and lots of things happen during that  
13 time that may dilute the true treatment benefit of the  
14 investigational product. So the limitations of this  
15 approach include little alignment with clinical  
16 practice, a narrowly-defined study population,  
17 relative late initiation of the investigational agent,  
18 and the evidence that is gathered and therefore the  
19 labeling that can result from the trial addresses a  
20 single infection site. So how can we address some of  
21 these challenges?

22                   Another way of pointing out the

1 differences between the trial structure and clinical  
2 care is to look at the timing of the treatment, the  
3 populations that are included, the motivating event  
4 that leads to the use of either the investigational  
5 product or the approved product in clinical use, the  
6 types of infections that are treated, and whether  
7 we're looking at non-inferiority or superiority. All  
8 of those things are relatively different between the  
9 clinical use and the way we study these agents. And  
10 those can increase the risk that we produce data that  
11 doesn't allow us to make the best-possible regulatory  
12 decisions.

13           So clearly new agents are needed to  
14 treat challenging organisms across multiple sites of  
15 infection. And in clinical practice, antibiotics with  
16 demonstrated penetration into the infected site and an  
17 appropriate antibacterial coverage are routinely used  
18 for infections at those sites, independent of any  
19 site-specific supporting data, and certainly  
20 independent of labeling.

21           Now, there has been, as we all know,  
22 problems with a surprising lack of antibiotic efficacy

1 at specific sites, most notably lung. And that's  
2 generated concern regarding sharing efficacy data  
3 across anatomic sites. When I talked to people who  
4 are deeply embedded in this area, there is almost an  
5 air of PTSD regarding the trials that resulted in  
6 these surprising findings. And that experience should  
7 not cause us to abandon the common clinical reasoning  
8 that an antibiotic that works well in multiple sites  
9 is more likely to work well at another site than an  
10 antibiotic that does not work well at multiple sites,  
11 but we also need to do so with our eyes wide open.

12 So the proposed strategy I'm going to  
13 discuss is a platform trial with enrollment timing and  
14 antibiotic initiation designed to match clinical use,  
15 careful integration of information across body sites -  
16 - and we'll spend quite a bit of time talking about  
17 what careful means -- that simultaneously addresses  
18 both noninferiority and superiority, because I think  
19 that choice is a false dichotomy, and may achieve  
20 additional efficiencies through the platform trial  
21 structure.

22 So the proposed trial would look

1 something like this in terms of flow. The patient  
2 presents with the signs and symptoms of a serious  
3 bacterial infection and is at risk for but does not  
4 have a documented infection with a highly-resistant  
5 organism. The patient is evaluated for participation  
6 in the trial as part of their emergency department  
7 evaluation, and the first antibiotic they receive is  
8 the randomized investigational product. At some point  
9 after that, they're admitted. And at some point later  
10 we get the results of the cultures, additional  
11 diagnostic tests that verify the actual site of  
12 infection and the resistance pattern of the organism  
13 or the fact that there is no isolate identified, and  
14 then the outcome is assessed.

15 And the question is how could we use  
16 data from this type of simpler structure to  
17 appropriately inform both regulatory decision-making  
18 and clinical decision-making regarding use of approved  
19 products. The advantages is that this aligns with  
20 clinical practice, there's a broad study population,  
21 there's early initiation of the investigational agent,  
22 and you will get information that informs you about

1 evidence across resistance patterns and across  
2 clinical sites of infection.

3           So first, what do we mean when we talk  
4 about a platform trial? So a platform trial is an  
5 experimental infrastructure that's intended to  
6 evaluate multiple treatments, often for a group of  
7 diseases. For a group of diseases here, you can think  
8 of different infection sites or different underlying  
9 pathogens. And the platform trial is intended to  
10 continue beyond the evaluation of any individual  
11 treatment. The treatments are often used in  
12 combinations. The trial explicitly incorporates the  
13 idea that the diseases that are being studied are  
14 similar to each other but not identical, and there's a  
15 dynamic list of treatments that are available.

16           So this terminology is borrowed from  
17 the oncology world. And I first want to make a  
18 distinction between a master protocol and a platform  
19 trial. The term master protocol is a very broad term  
20 that may include simply the use of very standardized  
21 clinical processes to increase the efficiency of a  
22 clinical trial. But the separate experiments within

1 the master protocol may be inferentially separate.  
2 You may be asking separate questions about completely  
3 separable populations or treatments.

4 A platform trial in contrast in my view  
5 incorporates some sort of statistical sharing of  
6 information to increase the efficiency of the  
7 inference given any particular set of data.

8 An umbrella trial is a term used then  
9 you're testing multiple different drugs for diseases  
10 that occur at the same site. And you may think of  
11 that as multiple studies of a pneumonia with different  
12 underlying etiologies or organisms.

13 A basket trial is a trial in which the  
14 disease shares a commonality that is a target of the  
15 treatment, but is in different anatomic sites. That  
16 would be for example sharing of information across  
17 body sites when you're using a single drug that's  
18 active against a particular class of organism.

19 There's a very nice review article  
20 written by Drs. Woodcock and LaVange that goes  
21 through this terminology and provides a very nice  
22 background.

1           So what is the proposed strategy? The  
2 patient presents with an infection in either the lung,  
3 the urinary tract, or the abdomen. But if you're  
4 interested in gram-positives, you could replace this  
5 figure with the places where gram-positives are of  
6 most interest and challenging. And from each of these  
7 sites, we obtain bacterial isolates, and we either  
8 identify them as being sensitive to the standard of  
9 care, resistant, or unable to be cultured. We want to  
10 demonstrate superiority to the standard of care among  
11 those patients who have resistant isolates. Non-  
12 inferiority to the standard of care control arm in  
13 those that are sensitive to the standard of care. And  
14 I put a question in there what you would do with those  
15 who have missing bacterial isolates. And we want to  
16 take advantage of the multiple body sites.

17           Over time, the agents that are being  
18 considered could also change. One could start with a  
19 control arm and maybe one, two, or three active arms.  
20 And over time, additional arms can become available.  
21 You may decide that based on additional safety data or  
22 other preclinical information, it becomes appropriate



1 to combine arms into a single arm. That's the A plus  
2 D. Arms may be discontinued for harm or futility at  
3 any point. And if one of the arms is demonstrated to  
4 be superior, that can seamlessly become the new  
5 standard of care in a platform trial without  
6 redesigning the trial. This addresses a point that  
7 John made about what happens if you identify a new  
8 standard of care; do you suddenly undermine your  
9 ongoing research efforts?

10 This approach has been modeled  
11 numerically through work that was supposed by the ARLG  
12 and others and involved a wide variety of  
13 collaborators. And in general if you consider this  
14 approach and you make reasonable but particular  
15 assumptions about the number of drugs, the fraction  
16 that are positive or negative, et cetera, you can save  
17 an average of something between 40 and 60 percent in  
18 sample size per answer you get regarding the  
19 superiority of the drug and resistance, isolates, or  
20 non-inferiority in sensitive isolates. And this  
21 efficiency comes from the shared control, the sharing  
22 of information across body sites, and the fact that

1 the study can seamlessly drop an arm for inferiority  
2 or for futility. And the assumption is that another  
3 drug is available to be tested. So that's a very  
4 particular assumption.

5 I want to specifically comment about  
6 the sharing of information between body sites. So we  
7 all know that antimicrobial agents are likely to have  
8 different effects at different body sites, for a wide  
9 variety of reasons. The question is whether the  
10 degree of variability in the treatment effect is  
11 clinically unimportant and we should think about the  
12 treatment effects as similar across body sites, or  
13 it's clinically important so we should think  
14 differently about the use of that drug across body  
15 sites.

16 So the question is how can we address  
17 both the possibilities that the treatment effects will  
18 be largely similar and that the treatment effects will  
19 be highly disparate in a single statistical model.

20 Clinicals do this sort of borrowing all  
21 the time. We take data that have been obtained in  
22 particular types of patients and we apply them to

1 others. But we do this in a way that is not well-  
2 documented and is not quantitative. Here we need a  
3 strategy that is completely prespecified, that is  
4 statistically rigorous, and whose operating  
5 characteristics can be evaluated numerically.

6           It is very tempting to try to avoid the  
7 reality that similarity is not an all-or-none thing.  
8 We tend to behave as if it is. So we will group all  
9 types of infections together if they were included  
10 within the inclusion criteria for a trial, or we will  
11 exclude them if they were not. We will include, for  
12 example, all different sorts of isolates if they were  
13 at least represented at all within the trail.  
14 Although we certainly don't have enough evidence to  
15 make independent estimates of the efficacy of the  
16 agent across each species of bacterium. For example,  
17 it was isolated.

18           The all-or-none approach puts us at  
19 tremendous risk of failing to identify subgroups that  
20 do experience different treatment effects of  
21 complications if we start by combining them all  
22 together. So we miss real differences that exist.

1 And we also fail when we separate them to recognize  
2 compelling circumstantial evidence of treatment  
3 efficacy. For example, if the drug works across four  
4 or five different infection sites, the chance it will  
5 work against the fifth or the sixth infection site is  
6 greatly increased.

7 So the approach that we'll talk about  
8 is a Bayesian hierarchical model. And I've underlined  
9 the key conceptual strength of this approach. The  
10 Bayesian hierarchical model shares information across  
11 subgroups, or in this case, body types, to the degree  
12 that is justified by the consistency of the  
13 information. So, contrary to something that is  
14 commonly stated, that you have to make an assumption  
15 about how similar the treatment effect is across body  
16 sites, instead what you do is you create a model that  
17 can learn how consistent the treatment effect is  
18 across body sites and use a greater degree of pooling  
19 if you see consistency and a lesser degree of pooling  
20 if you see heterogeneity of the treatment effect. So  
21 how does that work?

22 So consider a data set in which you're

1 enrolling three subtypes of infection and you get  
2 three separate point estimates if you simply looked at  
3 the treatment efficacy that appears to be present in  
4 each one of those three sites. Each one of those  
5 point estimates has some uncertainty around it. And  
6 the hierarchical model assumes that those treatment  
7 effects are themselves drawn from a population of  
8 treatment effects among lots of different body sites  
9 that might exist. And the hierarchy is an assumed  
10 distribution of body sites or subgroups, and there's  
11 uncertainty in how similar those subgroups will be to  
12 each other. That's the prior variability at the third  
13 level of the hierarchy. So you actually allow the  
14 model to realize you don't know how similar the  
15 treatment effect will be in the three body sites or  
16 the four body sites.

17           When the hierarchical model fits the  
18 data -- and this is sometimes called a shrinkage  
19 estimate -- it creates new estimates for the treatment  
20 effect in each of the body sites individually that  
21 learns from the consistency of the effect across body  
22 sites.

1           There is a very general statistical  
2 fact called the James Stein effect -- I put the 1961  
3 publication there just to show it's not new -- that  
4 says that the best estimate of a true treatment effect  
5 in a subgroup is actually not the treatment effect you  
6 get by simply looking at the data within the subgroup  
7 if there are three or more subgroups. This is a very  
8 general, non-Bayesian result that is horribly,  
9 horribly inconvenient because it is so  
10 counterintuitive. It means that when you look at the  
11 treatment effect in a type of disease for a drug, you  
12 should think about how well that drug works in all  
13 kinds of other similar diseases, just like clinicians  
14 do every day.

15           So how about the non-inferiority and  
16 superiority issue? The data that one would get from  
17 this proposed approach to a platform trial would  
18 include data when the infecting organism is isolated  
19 and found to be highly resistant, when it's found not  
20 to be highly resistant, and also you're going to have  
21 some patients who clinically appear infected for which  
22 you are unable to identify a specific etiologic

1 isolate.

2           The first data set from the patients  
3 who have isolates that are highly resistant can be  
4 used primarily to address a superiority hypothesis.  
5 It can secondarily be used to address a non-  
6 inferiority hypothesis if there is value in approving  
7 a drug simply because it's non-inferior to the  
8 comparator in that setting.

9           When the infecting organism is isolated  
10 but found not to be highly resistant, that can be used  
11 to address a non-inferiority hypothesis and also to  
12 address safety and PK and other goals.

13           When the patient has no isolate  
14 obtained, that can be used to address the non-  
15 inferiority hypothesis, but there are some very  
16 specific considerations there depending on the site  
17 and what a non -- a positive culture means in that  
18 setting. That would be a great thing to discuss at  
19 length another day.

20           But the point here is that the  
21 membership of the patient into each of these subgroups  
22 is based on a pre-treatment assessment, which is the

1 culture. So these are valid subgroups for which you  
2 can draw valid statistical inferences. This approach  
3 allows the early initiation of the investigational  
4 product before you know the subgroup into which the  
5 patient will fall, and more of the patients that you  
6 screen contribute data that informs clinically-  
7 important questions.

8 Agents should only be included in this  
9 sort of approach when there is strong learn-phase  
10 rationale, demonstrated penetration, PK, lack of  
11 inactivation at the site -- that's the PTSD from the  
12 lung example -- that makes it reasonable to test that  
13 drug in that site against the likely spectrum of  
14 organisms. But with this approach, each enrolling  
15 site -- meaning clinical study site, hospital, or  
16 whatever -- can contribute a larger number of patients  
17 per month because there are multiple infection types  
18 and resistance patterns included. And that decreases  
19 the per-patient cost and helps you support your  
20 network. The efficiency of the platform is increased  
21 when there is more than one investigational agent  
22 available at the same time for an indication because



1 of the shared control arm, but that is not necessary  
2 to achieve some savings. And the current environment  
3 with multiple smaller companies may be particularly  
4 conducive to a platform strategy.

5 I have a couple of slides which I've  
6 included in the site that have to do with labeling and  
7 stewardship. The point simply stated is that when we  
8 approve drugs that are most valuable from a public  
9 health point of view when their use is restricted to  
10 highly-resistant organisms but we label them for broad  
11 clinical indications, that that potentially undermines  
12 stewardship efforts. I don't want to dwell on this,  
13 because first of all, I'm not an expert in this area.  
14 But I do think that the statistical design drives the  
15 data, the data drives the labeling, the labeling  
16 drives the marketing, and we want to make sure that to  
17 the extent possible that that supports stewardship  
18 from a public health perspective.

19 So in conclusion, I think the most  
20 common structure in statistical design of confirmatory  
21 trials of antimicrobials risk failing to answer the  
22 questions that are of most direct clinical urgency and

1 impact. They fail to address the likely subsequent  
2 use of approved products across multiple infection  
3 sites, demonstrated only on the presence or risk of  
4 highly-resistant pathogens and hopefully PK and  
5 penetration data, but that a multi-infection site,  
6 multi-drug platform trial addressing both non-  
7 inferiority and superiority simultaneously could  
8 address those challenges. Thank you very much.

9 DAN RUBIN: Thank you. Our next  
10 speaker is Scott Evans. He is a Professor and  
11 Founding Chair of the Department of Biostatistics and  
12 Bioinformatics at George Washington University and the  
13 Director of the George Washington Biostatistics  
14 Center. He is also the Director of the Statistical  
15 and Data Management Center for the Antibacterial  
16 Resistance Leadership Group.

17 SCOTT EVANS: Thank you very much, Dan.  
18 And good morning, everyone. Thank you for the  
19 opportunity to talk with you today. I'm going to move  
20 quickly.

21 A couple of years ago, I had a leaky  
22 roof in my house. It created a water bubble in my

1 wall. It was a very strange-looking thing, but I had  
2 a water bubble in my wall. And in addition to a new  
3 roof, I had to repaper the wall. And my neighbor had  
4 recently papered a similar-size room in his house.  
5 And so I asked him how much paper did you buy. And he  
6 replied six rolls.

7           Upon finishing papering the wall, I had  
8 only used four rolls. And went to my neighbor and I  
9 said, listen, I had two rolls left. What happened?  
10 And he replied, oh, that happened to you, too?

11           Now, I tell you this story because I  
12 asked the wrong question. And I find in clinical  
13 trials we're often asking the wrong question as well.  
14 And as a matter of fact, the two things I've learned  
15 about antibiotic clinical trials since I've been  
16 involved with them. First of all, they're rigorously  
17 conducted by experts in the field, they closely adhere  
18 to highest standards and fundamental principles of  
19 randomized trials. And secondly, they're essentially  
20 useless for helping clinicians make treatment  
21 decisions. And so we've been working on ways to try  
22 to figure out how to rectify this.

1                   This was said perhaps more eloquently  
2 by the former FDA Commissioner Rob Califf. "Most  
3 clinical trials fail to provide evidence needed to  
4 inform medical decision-making. However, the  
5 implications of this deficit are largely absent from  
6 discourse."

7                   So the example uses we have in  
8 antibiotic trials is drugs are compared in susceptible  
9 disease, but susceptibility is not known until we  
10 actually start treating, after we've started treating  
11 the patient. Patients are considered failure when  
12 they change therapy, though they may not actually  
13 fail. We lose interest in patients that change  
14 therapy, despite therapeutic adjustments that could  
15 effectively treat the patient. Populations studied  
16 are not the same as the population applied. In non-  
17 inferiority trials much of the time we exclude  
18 patients with recent prior therapy. These drugs are  
19 then used in these patients, possibly representing a  
20 majority of these patients.

21                   There are further issues. We often  
22 define analysis populations in trials. Efficacy

1 analysis we define an intention to treat population.  
2 Safety analysis we define as safety population. Those  
3 populations are not the same.

4 We then combine these two analyses into  
5 what we call a benefit-risk analysis. But to whom  
6 does this benefit-risk analysis apply? We're  
7 estimating a parameter from a population that doesn't  
8 exist. Nobody seems to mind.

9 Another question. We measure duration  
10 of hospitalization, duration of the ICU stay in  
11 clinical trials. Shorter duration is better. The  
12 faster the patient dies, the shorter the duration. So  
13 you give me a summary statistic of duration of  
14 hospitalization, I don't even know what it means.  
15 Part of that's self-inflicted wounds by the way we  
16 design and analyze studies. Outcome interpretation  
17 needs context of other outcomes for that same patient.  
18 Once you tell me whether the patient lived or died,  
19 the number makes sense.

20 Question three. Trials typically use  
21 binary endpoints. For example, cure. The patient has  
22 to survive, their symptoms resolve, they have

1 microbiological eradication, no changes to therapy.  
2 But consider the following. One patient fails because  
3 they die. Another patient fails because they have a  
4 lack of micro-eradication. It would seem reasonable  
5 that now our primary analysis doesn't distinguish  
6 these two patients. Shouldn't a primary analysis  
7 recognize the difference of this? That would seem  
8 important enough to recognize.

9           This would seem to be particularly  
10 important recent FDA Advisory Committee for evaluating  
11 plazomicin in complicated UTI. The composite cure  
12 rate, 81 percent for plazomicin, 70 percent for  
13 meropenem. But if you just look at the clinical cure  
14 rate, very close. Right around 89, 90 percent for  
15 both. It turns out that the advantage for plazomicin  
16 is in the micro-eradication. That would be  
17 particularly important to know particularly when you  
18 start to look at the safety data that suggests, well,  
19 there's more safety concerns with plazomicin than  
20 perhaps with meropenem.

21           The last lesson I'd like to sort of  
22 motivate this is one plus two times three is not nine.

1 And grade school children know this, but the clinical  
2 trial community have missed this course. Let me  
3 explain what I mean by this. So here's a question for  
4 you. Supposed a loved one is diagnosed with a  
5 terrible infectious disease. You get to elect  
6 treatment. We have three treatment options; A, B, and  
7 C. All right?

8 Now, let's suppose there's two outcomes  
9 for simplicity. Let's assume they're equally  
10 important. You have treatment efficacy, treatment  
11 success outcome. Yes or no. The patient gets it or  
12 they don't. They also have a safety event. Patient  
13 experiences it, yes or no. Now, luckily enough, we  
14 had a randomized trial that compares A, B, and C that  
15 help guide our decision about which one we should  
16 choose. Had a hundred patients in each arm, A, B, and  
17 C. The treatment success rate is 50 percent in A, 50  
18 percent in B, and 50 percent in C. Now, the safety  
19 event rate is 30 percent in A, 50 percent in B and C.  
20 Which treatment do you want?

21 Well, they all have the same success  
22 rate. A has got the lowest safety event rate. B and

1 C are indistinguishable. Can't tell the difference  
2 between them. Clearly, we choose A. We're all  
3 reasonable people.

4 But instead, what we've done here if  
5 you evaluate what we've done here, we've taken the  
6 patients in the trial and analyzed the outcomes, the  
7 two outcomes. What I'd like to do is flip that upside  
8 down. Take the outcomes in the trial and tell me what  
9 happened to the patient; that the purpose of measuring  
10 outcomes in clinical trials is to tell you how the  
11 patients are doing. We seem to have gotten it  
12 backwards.

13 So if I take the outcomes and analyze  
14 what happens to the patients, there are four possible  
15 outcomes for what happens to patients. They get the  
16 treatment efficacy, yes or no, and they get the safety  
17 problem, yes or no, in combination. So let's look at  
18 the combination.

19 Well, it turns out in treatment A, the  
20 efficacy and the safety were uncorrelated. So there  
21 were 35 patients that experienced the treatment  
22 success and avoided the safety problem. But in



1 treatment B, they were positively correlated. So  
2 there's zero patients that had treatment efficacy  
3 without the safety problem. In treatment C, they're  
4 negatively correlated. So I've got 50 patients that  
5 experienced the efficacy without the safety outcome.

6 Now, one slide ago I couldn't tell you  
7 the difference between B and C. Now, we're supposed  
8 to be in an area of personalized medicine where we're  
9 doing personalized -- and I can't tell the difference  
10 between B and C. So our culture has been to use the  
11 patients to analyze the outcomes. Shouldn't we use  
12 the outcomes to analyze the patients? That's the  
13 purpose.

14 So as my father told me many years ago,  
15 the order of operations is important, and we haven't  
16 got the order right. And we may be missing things  
17 without realizing it.

18 So William Osler, the well-known  
19 clinician, said years ago, "The good physician treats  
20 the disease. The great physician treats the patient."  
21 And maybe we should be analyzing things that way.

22 So Dean Follmann at NIAID and I wrote a

1 paper describing some of these issues and how we might  
2 attack things from a different angle in doing so. A  
3 couple of years ago we wrote this paper, DOOR,  
4 Desirability of Outcome Ranking. Think about what  
5 those words mean; desirability of the outcome. And  
6 it's going to be a ranking. And what we do is we end  
7 up computing what we call the DOOR probability, which  
8 is a probability of a more-desirable outcome when  
9 assigned to one therapy relative to another therapy.

10 Now, if you're a clinician treating a  
11 patient or you're a patient and asking I've got to  
12 treatment options, you can ask for differences in  
13 means and difference in proportions and hazard ratios  
14 and relative risk all you want. But what is a more  
15 natural question to ask when I'm trying to figure out  
16 whether I should take one therapy over another? Well,  
17 how about the global probability that one therapy is  
18 better than another? Wouldn't this be intuitive? So  
19 although it may be foreign at the moment, that perhaps  
20 this may be intuitive in the long run.

21 So here's an example of an application  
22 of this. Should we use ceftazidime, avibactam, or

1 colistin for the initial treatment of infections due  
2 to CRE? And this was a paper published by David van  
3 Duin using some observational data from an ARLG study.

4 Now, the DOOR that was set up, a  
5 desirability of outcome ranking, an ordinal outcome.  
6 You see most desirable at the top. The patient lives,  
7 they're discharged home, everything's back to normal,  
8 they avoided major adverse events. Least desirable is  
9 at the bottom; the patient dies. But there's layers  
10 in between where some things go right, but not  
11 everything goes right. And the idea is if colistin,  
12 whatever colistin produces, patients fall into these  
13 categories wherever they fall. Can I get patients to  
14 migrate northward using CAZ-AVI to more desirable  
15 places and evaluate that. And that's exactly what  
16 happened in this particular evaluation. The DOOR  
17 probability is 64 percent that you're going to have a  
18 better outcome using CAZ-AVI than you are in colistin.

19 Now, how do you summarize this sort of  
20 patient journey, which is the next question if you're  
21 going to use DOOR? Now, before analyzing several  
22 hundred patients, you have to figure out how you're

1 going to analyze one. Now, clinicians are supposed to  
2 be doing this when they're treating patients, but  
3 we've got to get into the head a little bit more.

4 So there was an example strategy about  
5 how we might create this ordinal outcome. This was  
6 led by Sarah Doernberg at UCSF through another ARLG  
7 study. And we call this BAC DOOR, because this was  
8 for bacteremia. And what we did was we were  
9 envisioning we're going to do a staph aureus  
10 bacteremia trial. And we did a pretrial sub-study to  
11 try to figure out how we might create a DOOR in this  
12 particular area.

13 So what we did is we took 20  
14 representative patient profiles from a prior study  
15 that had benefits and harms and quality of life, and  
16 in a single paragraph we wrote down what happened to  
17 those 20 patients.

18 We then sent those profiles to 43  
19 expert clinicians that treat this disease and said  
20 rank them in terms of the desirability of their  
21 outcome. We didn't tell them how to rank them; the  
22 idea was to figure out what are they valuing in terms

1 of how they rank patients.

2 And then we examined the components  
3 that drive the clinician rankings and used that to try  
4 to create a DOOR outcome. And we came up in this  
5 particular case with six different levels.

6 Now, one thing we learned from this  
7 particular exercise. First of all, you for the first  
8 time begin to evaluate the cumulative nature of things  
9 that happen on patients. Now, if you examine one  
10 outcome at a time, you never see anything cumulative.  
11 We never look at it. But if a patient is having  
12 multiple bad things happening to them, then that  
13 should be recognized. That's how patients are  
14 experiencing these outcomes, and that we should be  
15 thinking about how to do that.

16 So some natural questions arise when  
17 you evaluate things like this. There are potentially  
18 unequal steps between these categories. We like to be  
19 able to recognize that. Perhaps the step to the  
20 bottom category, to mortality, is bigger than the  
21 steps above it, is larger than the steps above it. We  
22 can recognize that. There's also varying perspectives

1 among patients and clinicians regarding the  
2 desirability of these different levels, and could we  
3 recognize that. And we have done this sort of  
4 analysis. We proposed what's called a partial credit  
5 analysis, which if you've got these ordinal outcomes -  
6 - these are the four ordinal outcomes from the CAZ-AVI  
7 colistin example -- what you do is you say, well, if  
8 you have the most desirable outcome, you get a perfect  
9 score; you get a hundred. If you die, you get a zero.  
10 If you get in the middle, then you get partial credit.  
11 And there are some very natural ideas about how we --  
12 next natural question is what are you going to give me  
13 for partial credit. And we've been working on that  
14 particular problem and we've got some ideas for that.

15           The other thing that can happen with  
16 this is there's been this debate in infectious  
17 disease, this area of infectious disease for quite  
18 some time that says, well, who do I want to enroll in  
19 trials. And one theory says, well, don't enroll the  
20 very sick patients, because they're going to die  
21 anyway and you're not going to have any sensitivity to  
22 detect any sort of effects.

1                   On the other hand, people say, well,  
2                   don't enroll the very more healthy patients, because  
3                   they're going to recover anyway, and you're not going  
4                   to detect any effects, there's not going to be any  
5                   sensitivity. Well, in this particular case if you  
6                   look at things using a DOOR type outcome, you can  
7                   evaluate which patients are actually benefiting from  
8                   say CAZ-AVI over colistin. And in this particular  
9                   case, the most severe patients were the ones who were  
10                  benefiting over CAZ-AVI -- CAZ-AVI over colistin.

11                  Let me show you this idea in a little  
12                  bit in another example. This is the PROVIDE study,  
13                  another ARLG study, which was a prospective, multi-  
14                  center, observational study evaluating among  
15                  hospitalized patients with MRSA bloodstream  
16                  infections.

17                  The research question; what's the  
18                  vancomycin PK exposure target that's associated with  
19                  an optimal treatment outcome. All right? 265  
20                  patients in this study.

21                  Now, what we did is we set up a DOOR  
22                  outcome. Most desirable at the top says treatment

1 success, and you avoid major toxicity, acute kidney  
2 injury. Least desirable at the bottom is the patient  
3 dies. But there are gradations of patient response  
4 along the way.

5 So what we did is looked at DOOR  
6 outcomes by dosing quintiles. So the top dose there  
7 is the highest bar. And what you see here is a  
8 distribution of the DOOR outcomes by dosing quintiles.  
9 Highest dose at the top, lowest dose on the bottom.  
10 All right?

11 So the blue on the left-hand side is  
12 that most-desirable category, treatment success  
13 without acute kidney injury. The purple on the far  
14 right is mortality. So what are you getting as you  
15 increase dosing? What you get is toxicity. You're  
16 not getting more efficacy; you're getting more  
17 toxicity. So higher doses bring higher toxicity, but  
18 not greater treatment success. All right. So  
19 actually this particular paper came out today in the  
20 Annals of Internal Medicine using ideas like this to  
21 actually monitor patients during the course of say DMC  
22 monitoring.



1           So in ARLG 2.0 one thing we're hoping  
2 to do is to develop standardized, syndrome-specific  
3 DOORs for the major infections in this particular  
4 area.

5           My last point I would like to make.  
6 There's been some talk today about platform trials and  
7 so forth. And in the ARLG we actually evaluated a  
8 platform to try to get at more pragmatic answers to  
9 the questions that are most important for us. We  
10 called this SMART-COMPASS. And the idea is -- so  
11 SMART-COMPASS stands for Sequential, Multiple-  
12 Assignment, Randomized Trials for Comparing  
13 Personalized Antibiotic Strategies. So this is  
14 consistent with the strategy theme that Vance and  
15 others had talked about earlier. But it's actually  
16 quite flexible and very consistent with the way in  
17 which patients are treated. It addresses several  
18 types of research questions, including identifying  
19 optimal treatment strategies, it can evaluate empiric  
20 therapies, and it can evaluate definitive therapies,  
21 those that are likely to be licensure-type questions,  
22 and provide efficiencies compared to traditional

1 multi-arm trials. And it's very pragmatic in the  
2 sense that it really mirrors clinical decision-making.  
3 You can think of it as personalized medicine.

4 So I'm going to end with a quote from  
5 NBA coach Frank Layden, who had a player that was not  
6 producing. And Layden asked the player, so what is it  
7 with you, son? Is it ignorance or is it apathy? And  
8 the player looked at Layden and said, Coach, I don't  
9 know and I don't care.

10 So I say to you today that if people  
11 don't know, let's educate them. And if they don't  
12 care, then let's motivate them. And I want to thank  
13 my collaborators, Dean Follmann at NIAID, Dan, and  
14 Chip and Vance from the ARLG, and all the ARLG team.  
15 I have no doubt that you will enthusiastically applaud  
16 now because you're so relieved that it's all over.  
17 Thank you.

18 JANE KNISLEY: Okay. Our next speaker  
19 is Aaron Dane. He is a consultant statistician who  
20 has been investigating how to make the design and  
21 interpretation of antibiotic trials more feasible. He  
22 has been a consultant since April 2016 and has

1 continued to make such development more feasible.

2 AARON DANE: Thank you. So as has just  
3 been said, all I've been looking at is for a while now  
4 is seeing more and more that we talk about doing rare  
5 pathogen trials. So this is a bit different from some  
6 of the other presenters in that this is in that area  
7 where it's very hard to get very much information.  
8 But we seem to be stuck in that if we can get 50 to  
9 100 patients with a resistant pathogen in a pretty  
10 long timeframe, we've got nothing we can do with the  
11 data. Because we can't get to traditional statistical  
12 criteria -- so we run the trial and then we can't do  
13 anything with it.

14 So as a result of that, I've been doing  
15 some work with Professor Nigel Stallard at Warwick  
16 University where we've been looking at -- and he's  
17 taking ideas from the orphan drug area where how can  
18 we use that information a bit more readily and get  
19 something from the data, particularly in areas where  
20 very specifically we can't generate much more  
21 information.

22 So we have a technical problem.

1 Well, maybe while they're sorting it  
2 out what I'll do is just -- so what I'm doing here --  
3 the idea is can we get more from a small study when we  
4 haven't got the option of a bigger study? And what  
5 I'm looking at here is very specifically we're still  
6 talking about doing a randomized trial. So this is  
7 still randomized, it's still controlled. This isn't  
8 about external controls, but it's having done that  
9 because we still feel that's the best way to get some  
10 useful information; what can we do with the  
11 information we have got? Because as we talked about  
12 yesterday, at the moment we do the study and then no  
13 one can use the information. So it's just a way of  
14 doing something a bit differently.

15 Okay. Is it working? All right, okay.  
16 Try number two.

17 So these are my disclosures. And so  
18 this was a collaboration with Nigel Stallard in  
19 Warwick. He has done some work in the orphan drug  
20 area. So basically that was the idea here, was to try  
21 and take some of that thinking when you've got that  
22 limited population and see if we could apply some of

1 that. And Paul Newell and John Rex have also helped  
2 as we've worked that through to put some clinical  
3 perspective on that as well.

4 So I'll skip through this quickly. So  
5 in terms of the superiority studies, this has been  
6 covered a number of times. What I would say is the  
7 idea is if we could do superiority studies, we would.  
8 It makes things much easier and much clearer. So it's  
9 not that we'd rather do non-inferiority studies, it's  
10 just that they often not really stick. For the  
11 reasons that have been spoken about, we can't study  
12 ineffective comparators. The numbers are small just  
13 by definition, which makes it more challenging. And  
14 there's often at least one therapy with some degree of  
15 efficacy. It may be toxic, there may be various other  
16 reasons you don't want to use it. But it's not that  
17 we're often dealing with something that's completely  
18 ineffective.

19 And also from the societal point of  
20 view, we don't want to just be developing new  
21 antibiotics when we can show superiority; we want to  
22 do it before that time.

1           So this was really just to illustrate  
2 how quickly the numbers fall away when we're talking  
3 about resistant pathogen studies. This is just an  
4 example, it's made up. But it's this illustration  
5 that from 300 patients if you're trying to then focus  
6 on a very specific pathogen, your numbers fall away  
7 very quickly. And that's before you even talk about  
8 that pathogen being resistant to all other therapies  
9 and all the other comorbidities that may cause  
10 confusion. So this is why we still need to find ways  
11 of developing trials for non-inferiority setting as  
12 well as superiority, even when we're talking about  
13 resistant pathogens.

14           And I think the key thing is that a lot  
15 of the time we're developing this for tomorrow's  
16 patients. So it's for a future unmet need as much as a  
17 current unmet need. And that's why we have to do it  
18 this way.

19           And I think then what we need is find a  
20 way of saying, well, how can we develop something when  
21 we can only get a hundred patients? So what do we do  
22 with that information rather than saying, well, that

1 doesn't meet traditional statistical criteria, so we  
2 just can't do anything. So it's finding a way of  
3 getting some information -- the conversation yesterday  
4 was, well, these drugs are still going to be used, so  
5 it must be better that we provide some framework for  
6 whether that drug's effective even if it's not the way  
7 we would do that traditionally.

8           Something I'm not going to mention in  
9 this talk is the idea of the safety database. It's  
10 obviously an important element as well. And that  
11 would have to be considered. But I'm focusing on the  
12 efficacy aspect for this talk, but that would clearly  
13 be an important aspect as well.

14           So a possible approach to design of  
15 rare pathogens. So some of this is standard for any  
16 trial; what are we interested in when we run a trial?  
17 So we want to be confident that we can show an  
18 effective treatment works, and we want to be confident  
19 that we won't approve ineffective treatments. That's  
20 the premise of any trials, and that's a Type I error  
21 in power.

22           But the question is can we look at that

1 differently for rare pathogens and can we do that for  
2 example using some of the questions in the orphan drug  
3 area about understanding what extra information and  
4 value we gain from making the study bigger.

5 I think one of the key factors for me  
6 here is -- because often this discussion is saying,  
7 okay, it would be acceptable to do a small study, and  
8 that's all right. But actually we still need a  
9 framework for the decision-making. So as a sponsor,  
10 you need to understand what you need to show so you  
11 can understand the risks. These studies may be small,  
12 but they take a long time and they're very expensive.  
13 So we still need to understand how likely we are to be  
14 successful. And also just having clarity at the  
15 outset on what the decision-making is going to be  
16 means that it's much clearer to everybody what's  
17 needed.

18 So the aim here was to provide a  
19 framework in that setting where you've got other  
20 therapies that may be suboptimal, but they still have  
21 some efficacy. And what I'm going to go through, I'm  
22 going to step through some examples. And this is not



1 about performing an interim analysis or not about  
2 continuing on after the trial in a single-arm setting.  
3 What this is about is saying if you've got a limited  
4 population, you run a trial in part of that  
5 population, and then everybody else goes on to one of  
6 the two treatments. Either they go on to the test if  
7 it had a successful outcome, or they continue on the  
8 standard of care if your new treatment failed in the  
9 study.

10 The other thing, I've stuck to  
11 frequentist statistics here purely from the point of  
12 view that I'm talking about a different idea anyway,  
13 so I didn't want to get into the Bayesian side as  
14 well. But you could equally apply this with Bayesian  
15 methods, some of the things I'm looking at.

16 So the first question is large versus  
17 small trials with rare pathogens. So larger trials  
18 lead to higher power, so that's great. Right? You'd  
19 always want that. But what we have here is that if  
20 the trial is too large or it takes too long, what it  
21 deprives patients of a more effective therapy, and it  
22 also means it might not be feasible to develop the

1 drug in the first place.

2 But on the flip side, if the trial was  
3 too small, it may be more feasible, but then you end  
4 up with much higher chances that you're going to make  
5 the wrong decision, which clearly we don't want to do,  
6 either.

7 But the theme for all of this is how do  
8 we work with a small data set? Because that's all  
9 that's going to be possible. We're not going to be  
10 able to generate any more. And that part isn't really  
11 much of a choice. So can we show there's a sweet spot  
12 for the sample size where we get sufficient  
13 information and we're not going to gain a lot more if  
14 we keep going on with the trial? And really that's  
15 the idea of the diminishing returns outside of that  
16 sweet spot.

17 So what we're aiming for here, so if  
18 test is worse than control, then in that situation,  
19 every patient randomized to test in a trial risks a  
20 worst outcome. So if test is approved, we perpetuate  
21 that problem, and there's even more patients that are  
22 having a worse outcome than they would otherwise. So

1 the mitigation here is that we have a small trial, but  
2 we avoid or reduce that chance of incorrect approval,  
3 which is what we normally talk about as Type I error.

4 Equally, if a test is better than  
5 control, then every patient randomized to control  
6 risks a worst outcome. So in this case if test is not  
7 approved, then that's perpetuated. So you're still  
8 risking everybody having a worse outcome. So here  
9 within that small trial we want to keep the power  
10 high.

11 And then the third scenario I'll  
12 present is when test is similar to control. So in  
13 this case, we still want to make additional therapies  
14 available. So again, in this case within that small  
15 trial, we'd want to keep the power high.

16 The important part with all of this  
17 though, this all sounds fine and easy. But the fact  
18 is we don't know which of these three scenarios is  
19 true when we're designing a trial and when we're  
20 interpreting a trial. So this is where we need to  
21 understand the risks we have of all these things  
22 happening. So what are the risks that we incorrectly

1 approve a new drug, or what are the risks we miss a  
2 good drug by the criteria we apply?

3 So what this is presenting -- so I'm  
4 going to present three different scenarios, one for  
5 test being better, one for it being worse, and another  
6 one where it's the same to understand some of those  
7 risks.

8 So in this situation imagine that we've  
9 got a non-inferiority trial which is looking at test  
10 against control. The test response rate is 60 percent  
11 and the control is 40 percent. So what we've chosen  
12 is a non-inferiority margin of 20 percent here with a  
13 95 percent confidence interval. So we've already  
14 started with a wide margin because of the rare  
15 pathogen and the area of unmet need. So the correct  
16 outcome and what we want to say in this case is that  
17 we conclude non-inferiority.

18 So we run the trial. And the plot on  
19 the right shows the chances of concluding non-  
20 inferiority. And what it's showing is that from about  
21 40 or 50 patients per group, you've got a reasonable  
22 chance that you're going to show non-inferiority. So

1 80, 90 percent power. So you might need more for the  
2 safety database, but in this scenario what that's  
3 showing you is that you'd have a decent chance of  
4 success given that situation.

5           And then on the flip side, if the test  
6 was 20 percent worse than control, so if the response  
7 rates here were 20 percent and 40 percent, what would  
8 happen then? So we're still using the same NI margin  
9 and confidence interval, but in this case you don't  
10 want to conclude non-inferiority. And what that's  
11 showing is that the chance of concluding non-  
12 inferiority on the plot now is very low. So in this  
13 case, again, 40 or 50 per group would be okay for this  
14 situation. Because what it's showing is you rarely  
15 make the error of concluding non-inferiority.

16           And finally, when the test and control  
17 are the same, we have all the same setup. So this  
18 time they've both got a 40 percent response rate.  
19 Now, as you would expect, as the sample size gets  
20 bigger, the chances of concluding non-inferiority goes  
21 up. But what this is showing is that it would take a  
22 bigger study in this case to do that. So at 50 per

1 group, you'd only have a 50/50 chance of success even  
2 when you're actually truly the same as the comparator.

3 So around 80 per group may give you  
4 what you need. And it takes a long time to get beyond  
5 that. But I think the key question here is you'd need  
6 a substantial bigger study, and otherwise, you'd end  
7 up with a 50/50 chance for success.

8 And the reason I raise this is in some  
9 situations, that might be fine. It might be quite  
10 easy to get to 200 patients in one of these studies.  
11 But if it's not and you could only realistically get  
12 to about a hundred, a sponsor isn't going to put the  
13 time and money into a study if they've only got a  
14 50/50 chance of it succeeding.

15 So what I've gone through so far is  
16 sort of the more standard aspects of Type I error in  
17 power. But the other part that's been pulled through  
18 from the orphan drug area is what does this mean for  
19 patients after the trial. So in this case, suppose we  
20 had an overall population of patients with a rare  
21 pathogen. There's a thousand of them in total. And  
22 then if we include a hundred of patients in the

1 clinical trial, so 50 per arm, that means we treat the  
2 remaining 900 patients with whatever drug comes out of  
3 that study. So that means we have 50 patients on  
4 test, 50 on control, and then another 900 on one or  
5 other of the drugs depending on whether the trial  
6 concluded that the test was non-inferior or not.

7           And the purpose of showing this is that  
8 a bigger trial isn't always better with rare diseases  
9 when you're doing this. So if we assume we had a  
10 thousand patients with the rare pathogen and we had a  
11 hundred patients in the randomized trial -- and from  
12 what we looked at before, if we assume that we have a  
13 60 percent response rate for the test and 40 on  
14 control, as I showed before, what that means is that  
15 you would expect 30 of your 50 responses in the trial  
16 on test, and 20 out of 50 on control to respond. So  
17 that's the 40 and the 60 percent response rates.

18           And then dependent on whether that  
19 trial concluded non-inferiority or not -- so if the  
20 test was successful and got carried through, from that  
21 point, those remaining 900 patients you would expect  
22 to have 60 percent of them to respond. Okay? Whereas

1 if test failed, so you didn't conclude non-  
2 inferiority, that would mean that the standard of care  
3 would continue to be the treatment used. And so only  
4 40 percent of those 900 patients would now have a  
5 response.

6 And I won't get into all the details of  
7 the power and the probabilities of those two. But  
8 what you can then work out is the expected number that  
9 you expect to respond, which in this case would be 587  
10 of the thousand. So that's a 58.7 percent response.  
11 So that's fine.

12 But now then you'd say, okay, why don't  
13 we just do a bigger study? Because then we'd get more  
14 certainty that we have the right decision. But for  
15 this situation and this scenario, if you did the same  
16 thing with a trial of 400 patients, what happens now  
17 is you've still got the same 60 percent response on  
18 test and 40 on control, only with 200 patients per arm  
19 in the study now. And what that means is overall  
20 there's only 560 patients, or 56 percent of all the  
21 patients with this pathogen respond. And the reason  
22 for that is because you're waiting longer and you're



1 giving more patients the ineffective therapy before  
2 you switch to one therapy or another. So this is  
3 where the consequences can be worse for patients  
4 afterwards if this is the case.

5 So in terms of finding the sweet spot  
6 that I mentioned before, what we need to do is find a  
7 sample size we have a good chance of success when  
8 we're effective, low chance of approval when we're  
9 ineffective, and a reasonable chance of success when  
10 the two treatments are similar. But also consider  
11 this expected number of patients who benefit so that  
12 we maximize that. So the following plot summarizes  
13 that information.

14 So this is plotting out that expected  
15 chance of success. So here the top half is what I  
16 presented earlier, which is to say how often do we  
17 select the test agent. So when test is 20 percent  
18 better, we pick that pretty well from 40 per arm. And  
19 what the bottom plot shows is that a trial with 40  
20 patients, you ought to optimize that number of  
21 successes when you get to about 40 or 50 patients.  
22 And after that, it's diminishing returns because

1 you're keeping more patients in the study even when  
2 one of the treatments is less effective. So this is  
3 where you can then use this to look at that and say,  
4 okay, well, maybe 40 or 50 patients is reasonable.

5           Similarly, when test is 20 percent  
6 worse, what happens here is -- we already mentioned  
7 that the test is not selected very often. And again,  
8 the expected number of patients who respond drops  
9 right from the start in this case. And that's because  
10 in this case you run the study longer, and that means  
11 you're continuing to treat more patients on the test  
12 agent even when it's not effective.

13           So finally, the largest sample size for  
14 test is similar, as I mentioned before. So that goes  
15 up slowly. And you'd need to get to about 80 or a  
16 hundred patients pre arm before you'd get to a  
17 reasonable chance of success. In this case, the  
18 number you'd expect to respond stays the same. And  
19 that's because both treatments have got the same level  
20 of efficacy. So whichever one you choose, your  
21 expected response would still be 40 percent in this  
22 case.

1           So the reason I've gone through all of  
2           that is because what this shows is that 40 to 80  
3           patients per arm has reasonable power in these  
4           settings that I've shown. And that's assuming that  
5           the control has 40 percent efficacy and then the test  
6           has either 20 percent better or worse response.

7           But the fact is if the product has  
8           similar efficacy to the control at the moment, that  
9           needs more patients, a bigger study, which in some  
10          settings might be possible. But from what we've been  
11          talking about, that's not always going to be possible.  
12          So getting to 200 patients with rare pathogens is not  
13          always the case.

14          So if that's the case, how could we  
15          provide criteria when it's only feasible to recruit 50  
16          patients per arm, for example? And that could well be  
17          taking five years plus to get to that.

18          So one approach then would be to look  
19          at the plots that I've just mentioned, but use  
20          something like 80 percent confidence intervals rather  
21          than the traditional 95 percent confidence intervals.

22          Now, what I would specify here is that

1 this is in areas of large unmet need, and it would be  
2 very specific. So this wouldn't be a blanket approach  
3 to this. They would have to be specifically agreed  
4 that this is the idea that we understand the risk, but  
5 we do it in situations where the alternative is we  
6 have no data.

7 So I won't go through these plots in  
8 detail again. I'll save you all that pain. But what  
9 I'll summarize is that what shifts here is the  
10 observations that in this case is that when test is 20  
11 percent worse, the risk of approval goes up, the  
12 incorrect approval. So now it's about a ten percent  
13 chance that you'd conclude non-inferiority for a less-  
14 effective treatment. But when the test is similar or  
15 better, using the 80 percent confidence interval gives  
16 you a higher chance of success than using the 95  
17 percent confidence interval. And the pattern for the  
18 expected number of responses is similar to before.

19 So the important thing here is that  
20 this is example framework. So I'll give an example of  
21 using test and control being 20 percent better, 20  
22 percent worse. And I've given examples of 80 percent

1 confidence intervals. But the idea is this is a  
2 framework to say at the moment what we do is we say,  
3 well, we run a resistant pathogen study, and if it  
4 doesn't meet standard criteria, then we can't use it,  
5 and we know we can't get to those criteria. So this  
6 is a way of discussing what the unmet need is, what  
7 the feasibility is, and trying to get some idea of  
8 where we're going to be with some of these aspects and  
9 change some of the success criteria that we might have  
10 for these very specific situations.

11 So in summary, this is a framework to  
12 display the tradeoffs. So this is a situation when  
13 only a small trial is possible. So we need to  
14 understand the false positive and negative error  
15 rates, but we should think about whether we can change  
16 what those error rates are compared to a traditional  
17 area when we can study hundreds of patients. And the  
18 data on 100 to 200 patients can be very informative.  
19 And it feels like it's still better to generate that  
20 data and understand what it's telling us even if we  
21 have to acknowledge that the levels of risk and the  
22 level of information is not the same as we are

1 traditionally used to.

2           So in conclusion, I would say that the  
3 use of the power Type I error and the overall number  
4 of patients benefitting could be used to agree the  
5 sorts of criteria for these treatments of rare  
6 pathogens so that we get some information where  
7 everybody understands what we're going to see as a  
8 successful trial at the outset rather than us having  
9 to do the trials and then not really knowing what  
10 success is going to be until we get to the end of the  
11 study. Okay, thank you.

12           DAN RUBIN: Thanks, Aaron. We now have  
13 scheduled 15 minutes of Q&A and we'll go until 11:20,  
14 and I'd like to open up the Q&A for speakers for both  
15 sessions from this morning. If you'd like to make a  
16 comment, please just turn your card up, as was done  
17 yesterday. Try to get my attention or Jan's attention  
18 and we'll try to keep track of the order. Please, go  
19 ahead.

20           MANOS PERROS: Thank you. Just a  
21 comment and then a question. I find it shocking but  
22 not surprising that I believe, Vance, 87 percent of

1 the prescriptions in your institution for those new  
2 drugs were off-label. It's shocking. And I think we  
3 all need to decide whether we can settle for something  
4 like that or whether we want the labels to be more  
5 reflective of how the drugs are actually used. I  
6 would be in the latter camp but that's a discussion to  
7 have.

8           On the more specifics, I like the idea  
9 of registration trials, strategic trials. Let's  
10 remember that we also have other groups than  
11 prescribers and regulators that need to be satisfied  
12 in order for us to be in this business, and that  
13 includes pharmacists, P&T committees, payers, and who  
14 is going to -- what kind of data and what kind of  
15 information is (indiscernible) those groups.

16           And the bottom line of that is more  
17 trials take time and money that we don't have. Maybe  
18 Merck could do that. I don't know why they would but  
19 they could run. But we only launch a drug once. The  
20 price is set at launch. The trajectory in the first  
21 quarters is important. And while I love the idea, I  
22 think we need to think how we can do those kind of

1 trials before the drugs I launched.

2 VANCE FOWLER: Well, yeah, we can think  
3 about that all the -- you know, all the livelong day.  
4 I think that -- I mean, I think you... You know,  
5 what's that saying about don't let the perfect be the  
6 enemy of the good. I think we simply -- what I'm  
7 thinking about from a clinical standpoint is we need  
8 these drugs. You know, we need them today. And that  
9 87 percent, that's -- that is essentially -- if  
10 anything, it's maybe a little low. I mean, that's  
11 been... Mike Rybak published -- you know, you talk  
12 about ceftaroline a little bit more, for an example.

13 So, we've been -- you know, that  
14 compound, incredible compound in my opinion, you know,  
15 it's been handed off -- it's been owned by no less  
16 than five different entities so far. So, Cerexa, then  
17 it was Faris, then it was something that started with  
18 an A, then it was Allergan. And now Allergan's going  
19 away. I mean, so, you know -- and the likelihood of  
20 that -- of meaningful trials taking place with each of  
21 those handoffs plummets.

22 You know, Mike Rybak published a thing



1 from 2014, that's the best data we have to deal with  
2 it. It was a retrospective series of, I don't know,  
3 about 400 patients. Over 80 percent of those patients  
4 he described, and that was in 2015, were off-label.

5 So, that's the status -- I mean, that's  
6 the state of affairs in clinical care, treating drug-  
7 resistant pathogens in the United States. That's just  
8 the way it is. And so I don't see that, you know...  
9 And if we can go in and do trials beforehand, totally  
10 agree. I don't care when the trials get done,  
11 honestly, from a clinical standpoint, as long as the  
12 clinicians have the -- you know, can confuse the issue  
13 with facts about what we're actually doing, it's a win  
14 for the patients, right?

15 So, I'm just -- you know, what I'm  
16 trying to really propose is I guess maybe I'm saying I  
17 don't think it is going to happen, you know? Maybe  
18 I'm a pessimist. I usually am. I think that what can  
19 happen is we can get, you know -- that companies can  
20 get compounds through trials and complicated UTI and  
21 ABSSI or what have you, because it minimizes risk.

22 And then what I would like to see

1 happen in the next ten years, I do think clinical  
2 trial networks are the way forward. I feel what I  
3 would like to see is a means by which there -- that  
4 funding can be provided not just even from a single  
5 country but on a multinational perspective whereby  
6 everyone puts in a little bit, there's a means by  
7 which decisions -- responsible implementation of that  
8 precious resource can be applied to do the trials that  
9 have to be done.

10           So, yeah, maybe that's a little -- you  
11 know, big but, you know, someone's got to think big,  
12 you know, or we're just going to stay right where we  
13 are. It's the clinical -- it's the clinical community  
14 that's going to have to take on these tough-to-treat  
15 trials, you know, tough-to-complete trials because it  
16 just doesn't... You know, you guys have already got  
17 so much stuff just trying to stay alive that adding a  
18 -- putting your entire future on a single trial that  
19 is too -- that's never been done before, to me, is a  
20 bridge too far.

21           MANOS PERROS: Yeah. And, Vance, just  
22 to be clear, my point is not that -- I don't disagree

1 with anything you said. I'm not arguing that we  
2 should change the way those drugs are used. This is  
3 the right way to use them. But the point I'm trying  
4 to make is getting the drug approved is no longer  
5 enough for us to survive as an industry.

6 DAN RUBIN: So, we have a question  
7 online from John Tamico -- from John Tamico to Roger  
8 Lewis. We'll do that and then I've got Dr. Rex. So,  
9 the question, Roger, is "CIAI is partly a surgical  
10 disease, even resistant organisms can be managed with  
11 source control to the point host defense can clear  
12 infection confounding antibiotic effect. How is CIAI  
13 reliably informative across body site analysis?"

14 ROGER LEWIS: Okay, well, as a non-  
15 expert in this area, I think I'm going to take this as  
16 the general question of if there is reason to believe  
17 that a treatment is likely to be less effective in one  
18 setting than another, then that violates an assumption  
19 of exchangeability of the body site. So, one of the  
20 assumptions of a hierarchical model is that a priori,  
21 you're not sure which site the treatment effect is  
22 likely to be largest if you couldn't order them a

1 priori.

2           So, if you have reason to believe that  
3 an antibiotic is likely to be relatively less  
4 effective because of other things that affect outcome,  
5 then you have to adjust for that in some way. And  
6 perhaps pooling it doesn't make sense.

7           That said, what I would want to do is  
8 look at trials of treatments of antibiotics for  
9 complex intra-abdominal infection in which the  
10 isolates were sensitive and look at the magnitudes of  
11 the treatment effects based on the endpoints that were  
12 used, which presumably were compromised by the same  
13 effects, and see if it's really true that the  
14 treatment effect that we have observed from previously  
15 demonstrated efficacious antibiotics was really  
16 smaller to make that assessment.

17           DAN RUBIN: Thank you. Dr. Rex?

18           JOHN REX: Those were great talks. And  
19 back to you, Roger, this Stein-Lewis concept is almost  
20 causing my head to explode. And if I say it back to  
21 you it's that if I have a point estimate of some  
22 measurement, and then I have three point estimates of

1 three measurements, I'm actually -- the most valuable  
2 measure of my first point estimate isn't the actual  
3 number; it's actually a combination of the three point  
4 estimates. That seems to be the concept here that I  
5 can -- and the error in one direction might compensate  
6 for error in another direction, if I'm catching the  
7 drift of this.

8           And it seems to me that has some very  
9 interesting translations for us when we use -- you  
10 know, we focus on the one-off data -- that's my point  
11 estimate in CUTI. That's my... And it almost seems  
12 to suggest we're better off doing studies where we  
13 actually deliberately grab several different body  
14 sites as part of it and get -- and combine them. Or  
15 am I misunderstanding this? Talk -- talk a little bit  
16 more about James, Stein and their very  
17 counterintuitive concept.

18           ROGER LEWIS: So, the first has to do  
19 with understanding the difference between bias and  
20 estimation in treatment effect. So, the James-Stein  
21 theorem says that if what you're interested in is the  
22 error in estimating the treatment effect -- and I mean

1 error like mean squared error -- you get a lower mean  
2 squared error if you use information from all of the  
3 related things.

4           The -- it is not an unbiased estimate,  
5 okay, but the bias -- what you lose in the  
6 unbiasedness, in my view, in terms of the clinical  
7 utility estimate, is far outweighed by the benefit you  
8 get in the reduced noise that Dan mentioned.

9           So, the -- and you can think about it  
10 in the following way: Let's suppose you do a clinical  
11 trial and -- for a treatment in osteomyelitis, and  
12 there is a forest plot presented which shows the  
13 estimated treatment effect across all the different  
14 bones. You can't get to 206 but some large number of  
15 bones.

16           There is going to be some bone where  
17 the estimated treatment effect is surprisingly high or  
18 surprisingly low compared to all the other bones. And  
19 you as a clinician will look at that and know that  
20 that bone might be a little harder or easier to treat  
21 but it's probably not as much harder or easier to  
22 treat as the data suggests because there is the -- the

1 estimates that are particularly high and low are  
2 likely to be a combination of the true treatment  
3 effect being high or low and random fluctuation.

4           And what the James-Stein estimate or a  
5 shrinkage estimator does is it accounts for the  
6 expected variability in multiple measurements to give  
7 you an estimate that appropriately balances the  
8 evidence that one bone or subgroup is different than  
9 the others against the additional likely variability.  
10 That's what the shrinkage estimate does. When it does  
11 that, the distance between the estimated treatment  
12 effect and the truth, on average, is smaller.

13           So, what this means -- and I know  
14 there's a lot of people who do editorial work here --  
15 is that if you look at the forest plot or the table of  
16 subgroup effects in a clinical trial, that is  
17 fundamentally the wrong estimate if your goal is to  
18 give you the most accurate treatment effect estimate  
19 in each subgroup. It's fundamentally wrong.

20           LINDSEY BADEN: Yeah, but that's how we  
21 do it. I mean -- that's so interesting. Wow.

22           ROGER LEWIS: I wasn't debating what's

1 in print.

2 MAN 1: But that has its own  
3 assumptions.

4 LINDSEY BADEN: But people spin around  
5 --

6 ROGER LEWIS: So, the interesting thing  
7 about it is that the assumptions are extremely loose.  
8 And so the reason that this is not adopted as a  
9 standard approach I think has to do with a limitation  
10 in humans to understand situations where statistics  
11 work in a way that's counterintuitive. Just as if  
12 most people's experience doesn't include the fact that  
13 time slows down when things go really fast, okay? It  
14 just turns out to be true.

15 DAN RUBIN: I would just add on the  
16 James-Stein theory -- that the theory is that your  
17 mean squared error must improve if there's three or  
18 more subgroups. If you're talking about your average  
19 error or the sum of the errors across the groups, if  
20 there's any, you know, one outlying group, there's no  
21 guarantee that that, you know, within subgroup  
22 estimation must improve by bringing in other data --



1 although, you're right, that on average that shrinkage  
2 is going to be really helping you.

3 So, next we have Dr. Melnick and then  
4 Dr. Farley.

5 DAVID MELNICK: I just wanted to go  
6 back to a point that Dennis raised. You know, in a  
7 world where trial networks exist and there's a  
8 capability for early initiative of strategy-type  
9 trials, is there anticipated flexibility about the  
10 dissemination of that information?

11 You know, we need a mechanism for  
12 communicating that strategic information to the  
13 clinical community. And whether it's resistant  
14 pathogen trials or the application of a novel agent to  
15 bacteremia or something else, what -- how do we get  
16 that information out, you know, without incorporating  
17 that into the label?

18 MAN 2: (indiscernible) guidelines  
19 again.

20 CYNTHIA SEARS: Well, I don't know. I  
21 mean, guidelines is one approach but, Vance, you  
22 presented several examples where strategic trials are

1 published in the literature and disseminated. You  
2 know, it certainly would be helpful to clinicians to  
3 have more concentrated information so you don't have  
4 to go to individual facts. And also from the FDA  
5 documents, it sounds like there's readily available  
6 data early on that could be summarized while we wait  
7 for publication. Sorry I didn't leap up. I was  
8 thinking about it, but... I welcome other input,  
9 though.

10 DAN RUBIN: John?

11 JOHN FARLEY: Anything more on this  
12 thread? Because I'm going to change the subject to  
13 comparators. Anybody? So, Dr. Ucheo -- Uchea -- is  
14 that correct? Dr. Uchea?

15 CHIBUZOR UCHEA: Yeah.

16 JOHN FARLEY: So, we really appreciate  
17 you being here and appreciate Welcome's leadership in  
18 really focusing on clinical trial capacity in the  
19 areas where the pathogens of interest really are. So,  
20 both sort of where you're headed as well as actually  
21 some of the statistical methodologies which might  
22 allow for smaller studies -- it feels like they're

1 headed toward a -- using a comparator in those trials  
2 that may not be registered in those countries and may  
3 be expensive.

4 So, it may be early for you to ask this  
5 -- to ask this -- early to ask this question, but I  
6 wonder where you all are thinking about with that  
7 particular question.

8 CHIBUZOR UCHEA: Yeah, that is one of  
9 the things that we've been thinking about. In terms  
10 of comparators and standards of care, they vary quite  
11 widely within -- within regions. And especially where  
12 we're looking at as well, a big issue is availability.  
13 And that's one of the key reasons why we're looking at  
14 the interoperability of our network with other  
15 regional networks. And that will allow us to leverage  
16 the expertise in those areas and also potentially  
17 bring in the ability to use comparators that are known  
18 and have -- that we have sufficient knowledge about in  
19 other regions to be able to implement that into --  
20 into our potential region and have access to those  
21 compounds for use.

22 DAN RUBIN: All right. I do have a

1 follow-up to that issue. Just because of time, I  
2 maybe want to give you a follow-up and then go to  
3 Aaron, and then we'll go into the moderated  
4 discussion. But some of the later questions are big  
5 picture enough that I think they can address any  
6 issues here. But do you have a follow-up?

7           MANOS PERROS: Yeah, it is about the  
8 comparator but perhaps in the broader sense. I'm not  
9 a trialist. I'm trying to get my head around how this  
10 works. If you -- if you enroll a patient with  
11 pneumonia, at the point where you enroll him, you  
12 don't know if it's carbapenem (indiscernible) or  
13 carbon resistance, you don't know if it's  
14 enterobacteriaceae or pseudomonas. The standard of  
15 care in the comparator, it's different for each of  
16 those.

17           So, how does this work? A patient gets  
18 admitted, you don't start them on Colistin, but you  
19 would put them on Colistin the moment you diagnose  
20 CRE, for instance, in some regions but not in others.  
21 How do we do that in the clinical trial network  
22 context?

1 DAN RUBIN: I don't have the answer to  
2 that but, Aaron, did you have a comment? Or Dr.  
3 Uchea, did you want to follow up?

4 CHIBUZOR UCHEA: Yeah, that is one of  
5 the big problems that we know we'll be facing. It's  
6 something that we really have to look at. And we very  
7 much would value any additional input into that. But,  
8 yeah, that's one of the key tests that we're going to  
9 face.

10 AARON DANE: Yes. So, I just had a  
11 question for Scott, actually. So, Scott, I really  
12 like DOOR and what you can bring, but one of the  
13 things in terms of designing a trial with that as the  
14 primary endpoint is understanding the power and the  
15 risk of the study.

16 So, imagine a company's running a study  
17 and the company could sort of live or die by the  
18 outcome of that study -- and how you (indiscernible)  
19 and the assumptions you have to make. Because  
20 obviously with all the different categories, you've  
21 got to make a lot more assumptions than we normally  
22 would do, which is normally just what, response rate.

1           So, it's not using the approach, it's  
2 more how to assess the risk of the approach in the  
3 outset. I don't know if that's something you've  
4 looked at.

5           SCOTT EVANS: Yeah. Well, there's two  
6 ways to think about sizing the study depending on  
7 whether you want to size it based on a DOOR  
8 probability or a partial credit approach. And then,  
9 you know, as with any other hypothesis test, if you're  
10 going to do a hypothesis testing approach you've got  
11 to come up with a null and alternative. And the  
12 null's usually pretty obvious. But you've got to come  
13 up with what sort of effect size you want to see. And  
14 it's on a slightly different scale probability --  
15 you're better off in one treatment rather than  
16 another, or -- and you've got to either take that at a  
17 high level with just thinking at that probability  
18 level or think about how there's going to be a shift  
19 in the DOOR outcome between two treatments and try to  
20 size to detect it.

21           Or partial credit is basically you're  
22 on a continuous outcome. You can think of it as a --

1 as a difference in -- a difference in means or a  
2 difference in proportions on a 100-point scale.

3 VANCE FOWLER: May I add to that? A  
4 second element to respond to Aaron's very reasonable  
5 question would ideally be to standardize the DOOR by  
6 indication. And, in fact, sort of one of the early --  
7 sorry... So, the second strategy by which to avoid  
8 some of the challenges that Aaron raised would be to  
9 standardize the DOOR endpoint such -- by disease type.

10 And, in fact, one of the goals of ARLG  
11 2.0, one of the early initiatives that Helen, in fact,  
12 is hopefully going to be leading, if I can persuade  
13 her to, is to -- is to develop just that for the four  
14 most common anti-infective initiatives or approval  
15 pathways. So, intraabdominal, complicated UTI,  
16 HAP/VAP, etc. That could then be publicly available  
17 to all sponsors to utilize as -- probably an  
18 exploratory endpoint. I doubt you're going to get to,  
19 you know, a primary efficacy endpoint with a  
20 registrational setting.

21 But to make that available so that it's  
22 a common standardized tool that could then be employed

1 with whatever anti-infective agent may be at question.

2 AARON DANE: Yeah, I think something  
3 like that would be really helpful. And the reason I  
4 raise it is because we often have a lot of angst, even  
5 on what the response rate is. Yeah, and that's a very  
6 simple measure. And we're not sure -- and that's  
7 where a key risk can be.

8 So, if we're starting to move to three  
9 or four categories, which clearly makes sense, is  
10 clearly more sensitive, but then that means there's  
11 much more consideration and much more risk with that.  
12 So, anything that could help understand that in the  
13 disease areas would be good, I think.

14 VANCE FOWLER: And I think it's very  
15 likely that the factors, the conditions that impact  
16 one patient's clinical response for an intraabdominal  
17 infection is likely to be profoundly different from  
18 that that he or she would encounter in the setting of  
19 HAP/VAP or skin and soft tissue infection, what have  
20 you.

21 So, the notion would be that you'd  
22 create it carefully, validate it, and make it -- and



1 then essentially unleash it and make it, you know,  
2 publicly available for all sponsors to employ in their  
3 own development programs.

4 JANE KNISELY: Do you have a related  
5 point? Okay, go ahead.

6 RIENK PYPSTRA: Yeah, just to continue  
7 on that, you're suggesting to develop these DOOR  
8 criteria for the purpose of clinicians. But as we  
9 discussed before, we have other people who are  
10 interested in this. In your talk, Scott, you  
11 mentioned patients. I think that is important. But  
12 we have in between category as well -- the payers, who  
13 are very important decision makers.

14 So, if we include a DOOR outcome or  
15 analysis in our studies, which ones should we then  
16 include? Of course, we want to serve the clinicians  
17 but can we include another for the payers? Only to be  
18 concordant?

19 VANCE FOWLER: Yeah, sorry, I actually  
20 meant the intent and the intended audience of these  
21 DOOR Tools would primarily not be the clinicians but,  
22 rather, would be industry. Because the goal is to

1 make available a tool much along the same lines as a  
2 guidance. Think about the guidance for HAP/VAP or  
3 ABSSSI or what have you. That this is a tool that --  
4 you know, Compound A, Compound B from Company A and  
5 Company B, rather than create their own, have to go  
6 through their own validation, etc., that this is a  
7 standard external template against which to compare  
8 the performance of that compound.

9                   RIENK PYPSTRA: But the way to build it  
10 --

11                   VANCE FOWLER: The audience is -- the  
12 audience is indeed industry.

13                   RIENK PYPSTRA: Yeah. But the way to  
14 build it we heard from Scott that it was 43 profiles.  
15 They submitted it to clinicians, they came to six  
16 categories. I suppose if you submit those 43 profiles  
17 to a payer, he may -- they may come up with a  
18 different categorization. And so that's what I want  
19 to bring in here, and it's actually a question to  
20 Scott. Is that something that you've considered and  
21 that is possible or what do you think about it?

22                   SCOTT EVANS: Yeah. Well, the example

1 that I showed, we survey clinicians. But one of the  
2 questions we get is well, maybe you should survey the  
3 patients. Sometimes we forget about them in clinical  
4 trials. I think -- so, two comments: One is I think  
5 you could have multiple outcomes if -- in the sense  
6 that if clinicians, or industry, or patients, or  
7 payers are interested in different outcomes, you can  
8 construct those different outcomes and analyze them in  
9 studies.

10 One thing that we have done already  
11 with the DOOR outcomes in various studies is when  
12 we've implemented, for example, a partial credit  
13 analysis approach, although pre-specification and  
14 transparency is always the -- you know, so important  
15 in clinical trials, when it comes to putting a value  
16 on different outcomes, it seems to be avoided like the  
17 plague.

18 And it's a very interesting dichotomy.  
19 Transparency and pre-specification, but when it comes  
20 to writing down a value or trying to value different  
21 outcomes, nobody wants to touch it.

22 Now, acknowledging the fact that,

1 Number 1, that not everybody has the same value  
2 system, including payers versus clinicians versus  
3 patients, or even within those categories, the 20-year  
4 old woman is going to have a different value system  
5 than the 70-year old man, and to acknowledge that.

6 Now, one thing that we could do, as we  
7 get our DOOR outcome, we say we want to implement a  
8 partial credit approach. So, if I surveyed the  
9 clinicians and said, well, give me your grading key,  
10 and as -- to adhere to transparency and pre-  
11 specification, I could survey experts in this field  
12 and come up with sort of a population average of what  
13 people feel a grading system should be.

14 However, the actual analysis can also  
15 portray that if you want to deviate from that value  
16 system and would like to do some other value system, I  
17 can show you what the treatment effect is under that  
18 value system. And we have examples of this. In the  
19 CAZ-AVI Colistin study we did exactly this. And so,  
20 there are some mechanisms by which you can get  
21 information about that value system. One is to survey  
22 patients or clinicians or whatever the case may be.

1 The other is to get it in the course of the trial.

2           So, during the course of the trial, if  
3 you implemented, for example, a quality of life  
4 instrument, and I set up a DOOR outcome. And if I  
5 look at the patients in the most desirable category,  
6 those patients give me an idea using this quality of  
7 life instrument -- they give me an idea of what their  
8 quality of life is like.

9           Then I look at the quality of life in  
10 the patients in the second most desirable category and  
11 that perhaps in using this instrument, that the ratio  
12 of the quality of life of those patients compared to  
13 the patients in the most desirable category gives me  
14 an idea about how to score it with information coming  
15 directly from the patients themselves about how you  
16 impacted their life.

17           So, there's ways I can get patient  
18 information, there's ways I can survey, if you want to  
19 go to payers and other people, or go to clinicians who  
20 treat this disease, you can get that sort of  
21 information. Don't be fooled that all of them are  
22 going to have the same answer. And so the idea is, is

1 to collect that information, design and analyze trials  
2 using that information, but acknowledge the fact that  
3 people value things differently. That's life. That's  
4 the way it is.

5 But I can show you how two treatments  
6 contrast each other according to any particular value  
7 system we like. And we have examples of this.

8 JANE KNISELY: Okay, so I have Rebecca  
9 over here has been waiting patiently, then Helen, then  
10 Nick, then Roger, then Pam, then John. And we're all  
11 on the DOOR question.

12 DAN RUBIN: And Sumathi told us to just  
13 keep this discussion rolling since the next questions  
14 are kind of related. We're getting at those anyway.

15 JANE KNISELY: Great. Okay.

16 REBECCA REINDEL: Just to follow on the  
17 DOOR tool, which I think is a really interesting way  
18 to look at benefit risk together. In the setting of a  
19 known safety risk for a product where you use the  
20 partial scoring system to assess the benefit and the  
21 risk of that specific safety concern -- with the  
22 development of tools that are standardized for a given

1 body site not allow you to be flexible in terms of  
2 assigning risk for specific safety concerns for a  
3 given product.

4 SCOTT EVANS: I'm not sure I completely  
5 understand your question. But one point that came up  
6 as I was trying to understand your question. When  
7 you're identifying endpoints and constructing a DOOR -  
8 - so, the big concern in the room is if I take -- if I  
9 try to construct some sort of ordinal outcome, could I  
10 manipulate in such a way that I make my drug look  
11 better than yours because of the way I construct it,  
12 perhaps favoring some components of outcomes more than  
13 others.

14 So, the outcome you're after is the  
15 outcomes that are sort of important and valuable to  
16 patients. They're not necessarily -- although,  
17 obviously, you're evaluating toxicity associated with  
18 particular interventions. But what you're measuring  
19 is patient outcomes and things that are important to  
20 the patient. So, I want to make sure that when I  
21 construct it, I'm not just including safety events  
22 that happened to occur with this intervention, which

1 would -- but not this other intervention. Because if  
2 another intervention, your control intervention has  
3 got their own sort of toxicity risk, if I either  
4 emphasize those or deemphasize those, I'm not playing  
5 a fair game.

6 So, what I want to measure is those  
7 things that are important for patients or that we see  
8 that perhaps patients aren't aware of, but do it in a  
9 fair way, not so specific to the intervention,  
10 obviously there's some toxicity concerns you want to  
11 do with that.

12 But if you're going to be transparent  
13 and open about how to construct it, of course, the  
14 concern of regulators and the concern of the audience  
15 and people is that you don't build an outcome that is  
16 artifactually going to make you look better than the  
17 next guy because of the way you do it. It's got to be  
18 about meaningful evaluation of what's happening to the  
19 patient.

20 HELEN BOUCHER: So, I just had a small  
21 comment about the ability of DOOR, by route of Scott's  
22 comment, to include aspects of the outcome that are



1 more safety related and for which there are values  
2 that payers care about. And so, as opposed to the  
3 traditional non-inferiority trial where we have kind  
4 of the standard safety display, DOOR could provide the  
5 ability to measure in clinical meaningful ways that  
6 payers care about things like renal failure and things  
7 for which there's not only mortality but also cost,  
8 that people agree on that could help add to the value  
9 of a product, even if it doesn't add to the  
10 indication, specifically.

11 NICK KARTSONIS: So, I've been thinking  
12 about this door thing for many years now and I  
13 actually find it very intriguing and actually think  
14 it's a fascinating way to kind of think about marrying  
15 up both the efficacy and safety aspects that kind of  
16 go into the development.

17 And I do agree, I mean, trying to get  
18 the patient perspective and the payer perspective is  
19 important. But I will tell you with every country now  
20 having its own HTA agency trying to get agreement from  
21 payers is almost impossible. But, I mean, I do think  
22 we're also in a very unique situation that we've done

1 all these clinical studies over the last decade and we  
2 should learn from them.

3 And so I guess I had two questions, and  
4 it's probably more, you know, directed to the FDA and  
5 their perspectives on this. One is you guys have had  
6 conversations with other regulatory agencies. Do you  
7 think they would be open -- I'm trying to think about  
8 this now, also trying to make Japan happy and Europe  
9 happy -- would they be open to that?

10 And second is, is there a possibility  
11 to use all these datasets that have been generated  
12 that you guys have access to and do these sort of  
13 analyses in a way that doesn't de-identify the  
14 comparators, if you know what I'm getting at -- but  
15 helps provide information that has value from an  
16 endpoint standpoint?

17 So, I know it's a bit of a loaded  
18 question but I'm just curious. Because I do think  
19 it's an interesting way to think about things moving  
20 forward.

21 SUMATHI NAMBIAR: So, for the first  
22 question we haven't had a lot of discussion about DOOR

1 endpoint. At least -- more recently we've been  
2 involved with one product. We've had a couple of  
3 discussions. And in one of those discussions the EMN  
4 was part of the meeting, so we met with the company  
5 together.

6 I don't think we heard any sort of  
7 concerns in broad terms but it's more the details.  
8 And that's exactly what we were struggling with -- you  
9 know, what were the different components of the  
10 proposed endpoint? And so I think there is certainly  
11 a willingness to work. I just cannot speak for them  
12 and say they will agree.

13 But what I did not hear at the meeting  
14 was we just cannot move forward with this. But I  
15 think for us, the bigger struggle was really defining  
16 which of the components were appropriate and how one  
17 could actually discern because it was so -- again, I  
18 don't have a lot of experience, but this one example  
19 that we worked through, I think, between the different  
20 categories there was very little separation. And the  
21 subjectivity that was involved in putting them in one  
22 category or the other was certainly concerning.

1           But there is room to improve and refine  
2 that and we're working to do that. So I think -- Dan,  
3 is that a fair assessment?

4           DAN RUBIN: I think that's fair. And  
5 as far as using the existing databases to try to come  
6 up with a better outcome, I mean, there's some  
7 precedent for that through the FNAH project to look at  
8 different datasets and try to define endpoint, but I  
9 don't think there's been any discussions about using  
10 datasets to try to inform more ordinal types of  
11 scales.

12           SUMATHI NAMBIAR: So, as a follow-up,  
13 Nick, so you meant not de-identifying the data  
14 actually -- and that's where it gets a little  
15 difficult, right?

16           NICK KARTSONIS: That's always the  
17 tough issue, right? I mean, I'm speaking obviously  
18 only for Merck but I imagine my counterparts might  
19 feel similarly around it.

20           But on the flipside of it is it's  
21 hypothesis generating, right? It's not hypothesis,  
22 you know, proving. So, in some ways you could make a

1 case for helping to move the field forward. And  
2 you've done that, right, with -- thinking about non-  
3 inferiority margins and how you guys came up with M1s  
4 and M2s and all that, which was incredibly helpful for  
5 the field moving forward. So, I just raise that as --

6 SUMATHI NAMBIAR: Good thought.  
7 Certainly something we can talk about.

8 ROGER LEWIS: So, I think the  
9 discussion about DOOR and the difficulties of, you  
10 know, everybody agreeing on, for example, the relative  
11 weights or even the ordering of different outcome  
12 states is interesting. I think it's an example where  
13 the more sophisticated approach to patient outcomes  
14 illustrates problems with existing outcomes that we've  
15 been able to not have to face.

16 So, for example, if you use 30-day all-  
17 cause mortality, some people die in three days in the  
18 ICU, some people die at day 29 in the ICU, some people  
19 wish they were dead but they're still alive in the  
20 ICU. And different people would value those outcomes  
21 in a different order. But somehow 30-day all-cause  
22 mortality just feels really solid. But it's the same

1 illusion.

2           So, I think the discussion about DOOR  
3 is really important and illustrative but I wouldn't  
4 want it to be seen as a criticism of the approach. I  
5 think the approach is absolutely solid. The right  
6 thing to do. And at some point you just have to --  
7 for the purpose of defining the endpoint of a trial,  
8 defining the statistical characteristics and what  
9 defines an adequate and well-controlled trial, agree  
10 on what the order of categories are by disease state,  
11 just as Scott suggested.

12           But the fact that we don't have those  
13 same level of discussions for the rich outcomes that  
14 occur in the people who do or do not die in 30 days,  
15 that's just because we're choosing not to have those  
16 discussions, not because the same considerations don't  
17 exist.

18           JANE KNISELY: I think I have Pam next.

19           PAMELA TENAERTS: So, I think this is a  
20 fascinating way to look at a novel endpoint and I  
21 really think there might be a need for something to  
22 supplement the mortality, which is sort of

1     unidimensional in many ways.

2                     But what I would say is there's  
3     opportunity for confusion if you do DOOR as per the  
4     physicians, DOOR as per the patients, DOOR as per the  
5     payers, and then you're kind of like, well, which ones  
6     weigh more in the decision?

7                     So, my thing would be well, combine  
8     them all and come to a consensus where everybody -- it  
9     might be lower but everybody can agree to it. And I  
10    think that might be, you know, baby steps instead of  
11    sort of setting a new thing and potentially creating  
12    additional confusion.

13                    VANCE FOWLER: Yeah, agree. And, in  
14    fact, one of the sort of work streams that's intended  
15    is obtaining the -- essentially, a patient-assessed  
16    quality of life assessment for those same four  
17    indications. We've already done it with staph aureus  
18    bacteremia and gram negative bacteremia where we  
19    establish quality of life in those patients.

20                    And what was striking was two things.  
21    I guess the clinicians in the room would probably  
22    guess that the impact -- my hypothesis was that staph

1 aureus is going to -- it doesn't tend to kill you  
2 right away, it just sort of chews on you a long time.  
3 And that's exactly what you found -- that these  
4 patients who had ostensibly had been evaluated as  
5 cures, when you interviewed them extensively, you  
6 know, six weeks later or what have you, they were  
7 talking about, you know, terrible impacts on their  
8 lives. Having to wear Depends because they can't get  
9 to the bathroom in time. I mean, a profound impact on  
10 the quality of life. And these were ostensibly cures,  
11 what would've been cures.

12 So, and for gram negatives, it was  
13 really all about the first two weeks. If they're done  
14 in two weeks, by six weeks their quality of life is  
15 much higher than that with staph aureus.

16 So, yeah, incorporating that element,  
17 that's, again, part of the intent of creating this  
18 DOOR endpoint, is building patient assessment into  
19 that step forward.

20 JANE KNISELY: John Rex?

21 JOHN REX: So, the build I've got  
22 around DOOR here is that there -- I hear the plea



1 about people don't want to rate the number -- they  
2 don't want to put a number on it. There actually has  
3 been work done that I think maybe we just need to  
4 leverage it better. And I'm looking right now at the  
5 University of York and the University of Sheffield  
6 report that the U.K. is using to construct its value  
7 arguments around conducting a pilot program of buying  
8 new antibiotics. And there's a whole bunch of stuff  
9 in here about health-related quality of life and how  
10 you might think about measuring that in the setting of  
11 any infections.

12           And I've not decoded all of it and  
13 thought it through, but it actually makes me think  
14 further back to the ERG report from three or four  
15 years ago where I first learned about the value of a  
16 statistical life here and the way that the actuarial  
17 community estimates the value of staying alive for a  
18 period of time, and it feeds into the quality adjusted  
19 life here concept.

20           So, there are some tools that exist  
21 that would be familiar to the health technology  
22 assessment world that we may not know about. And so

1 my thought here about DOOR is, it's very interesting -  
2 - and that plot about the vancomycin showing that the  
3 lower exposures were actually net better, at least  
4 from my perspective, extraordinary.

5 So, this notion that the ID community  
6 needs to start folding in some of those measures --  
7 and I'm just compliant that some of it exists and  
8 that's the theme here. We need to borrow that  
9 information and apply it here.

10 AARON DANE: I was just going to say in  
11 relation to that as well, the other area where there's  
12 a lot of work done with quantitative benefit-risk  
13 assessment, which I think we should look at as well  
14 for the same reasons. Because that's all about being  
15 very clear on what the trade-offs are, and you're very  
16 explicit about how you weight them and you can look at  
17 what happens if you change the weighting. So, I  
18 think, again, that's something which is similar which  
19 we can draw on.

20 SCOTT EVANS: Yeah, just one comment to  
21 that. Thank you for the information about the quality  
22 of life. DOOR has been used in other disease areas,

1 including stroke prevention trials, for example, where  
2 there has been a lot of quality of life valuation  
3 about what happens to patients -- strokes, MIs, and so  
4 forth, where primary endpoints trials are time to  
5 stroke, MI, or death, or maybe something else.

6 But deaths are worse than strokes,, and  
7 strokes with permanent consequences are worse than  
8 things that are transient, and you can factor in  
9 bleeds and all that sort of stuff. And there has been  
10 scoring systems set up in that area and/or analyses  
11 that have used that information.

12 AMY LEITMAN: So, I wanted to address a  
13 few points that were discussed just from the  
14 perspective of somebody who's sort of getting  
15 entrenched in the world of PROs and PRO development  
16 because it's difficult to get patient feedback and  
17 looking at the different kinds of infections.  
18 Survival is not enough for a patient. That's really  
19 the goal, right, when you're treating a patient?  
20 Generally speaking, you do want them to survive.

21 And I heard what was said before, that,  
22 you know, what a patient wants when they're 20 and

1 what a patient wants when they're 70 or 80 or 90 may  
2 be different. And you may get to a point where a  
3 patient decides that they are not willing to continue  
4 on a journey. But, generally speaking, the goal is  
5 for the patient to live, to survive the treatment and  
6 survive the infection. But you're not treating an  
7 infection, you're treating a patient. So, how they  
8 survive matters.

9           And I think what we see when we are  
10 dealing with patients, a lot of times what we see, and  
11 maybe this isn't seen as much with the ID physicians  
12 because the follow-up is done by another physician  
13 probably. And maybe it should be done more by an ID  
14 physician so they could assess how the patient is  
15 doing. And it might be an easier way to catch if  
16 there's going to be a reinfection, there might be  
17 earlier signs that a physician could catch.

18           But you have to look at how that  
19 patient is doing. And so often we see them and it's  
20 just -- they still feel like a train wreck. And it's  
21 months and months later -- and this is with all kinds  
22 of respiratory infections, and then you have to deal

1 with skin and soft tissue infections. If there's been  
2 a surgical debridement, don't assume that there's no  
3 permanent impact. They're worried about disfigurement  
4 and they have to live with that impact.

5 And, you know, we actually deal with  
6 that with NTM. We catch the patients who are  
7 disseminated NTM and, unfortunately, they've gone to  
8 those, you know, cosmetic surgery centers and gotten  
9 those infections and I mean, there were I think 17  
10 deaths in New York City alone last year from that.  
11 And that's, I'm sure, not the only pathogen that's  
12 causing these infections.

13 So, you really -- you know, even if  
14 it's like an abscess on a limb, if it gets really bad,  
15 at some point you start thinking -- they start  
16 thinking am I going to lose my limb? Like, what's  
17 going to happen? So, there's a lot going on.

18 And then after that, let's say it's  
19 something with an abscess, you clear the abscess, it  
20 heals. Every little thing they become paranoid about.  
21 And it's something -- they get a bug bite and it's,  
22 oh, what's going to happen? Is this going to happen

1 again? What am I going to do? Are they going to be  
2 able to treat it?

3 So, it's really important to understand  
4 the patient journey, not just at the start of it, not  
5 just while they're going through the critical event,  
6 but afterwards. And really not just a month  
7 afterwards. For some of these patients it continues  
8 months or even years afterwards. Their body has  
9 undergone really a brutal assault. Some of these  
10 medications are really hard to take. Their immune  
11 systems have completely gone haywire trying to fight  
12 this infection. They're exhausted. They probably are  
13 having some kind of a nutritional deficiency, because  
14 when they're fighting an infection, they're just  
15 burning through calories.

16 You know, one of the things that our  
17 organization is starting to develop is a pamphlet on  
18 mental healthcare and a pamphlet on nutrition care for  
19 infection because those are things that patients have  
20 asked us for. And when I've talked to -- you know,  
21 I've talked to a sepsis survivor who was like, you  
22 know, the nutrition thing would probably be helpful

1 for people like us, who, when we're coming out of  
2 this, they've lost so much weight and they need  
3 guidance on not just how to put on weight but how to  
4 do it healthfully.

5 Like, you can't just pile in Ben &  
6 Jerry's as much as we'd like to. They can't just keep  
7 eating Ben & Jerry's all day. They have to figure out  
8 how to balance... You know, yes, you can have some of  
9 that but you have to balance the good nutritional  
10 intake and put those calories back on, and give your  
11 body what it needs to heal as well.

12 There was one other thing I wanted to  
13 talk about with respect to payers, and this is  
14 something that I'm seeing a lot in the patient  
15 advocacy community. So, the Institute for Clinical  
16 Effectiveness & Review, ICER, has a standard that they  
17 call Quality-Adjusted Life Years, QALY, or "Qually" as  
18 we call it. They start looking at various treatments  
19 and whether those treatment costs are justified by  
20 quality-adjusted life years.

21 And one of the things that we're  
22 dealing with now is that antibiotics are not

1 compensated well enough. And we're looking at  
2 developing these novel treatments, and it's really  
3 expensive. And these treatments are going to be  
4 expensive, and it's justifiable considering the cost  
5 and considering the value to society.

6 But we're talking about some of these  
7 infections like they are rare diseases. One of my  
8 concerns is that we'd better start bringing payers  
9 into the fold on this conversation as well as patients  
10 because I can guarantee you at some point down the  
11 road, ICER will turn its attention to some of these  
12 treatments and say, well, but, you know, two years  
13 later, they're still -- they're still really sick or  
14 they're getting sick again, they're getting pneumonia  
15 again. That is not -- I mean, believe me when I tell  
16 you that patient advocacy groups will kick up a huge  
17 fuss because any time this happens, it just seems like  
18 a particular group ends up getting targeted.

19 The patients suffer most. It's really  
20 up to the patient to decide what the quality of life  
21 is that they want afterwards, you know? Is the  
22 quality of life that they're going to get from the



1 treatment acceptable?

2                   And I just wanted to -- you know,  
3 Roger's point about 30-day all-cause mortality really  
4 goes back to measuring out over time with PRO.  
5 Measuring out 30 days isn't enough. Measuring out 60  
6 days might not be enough...90 days. So, it's -- we're  
7 at that point now where we have to start asking these  
8 patients what is your journey like? How long is it  
9 taking? Because when we start incorporating patient  
10 input into these clinical trials and we start  
11 measuring with PROs, one of the most important  
12 questions -- and this is the one that we're grappling  
13 with now, it's one of the many -- how long do we  
14 measure out?

15                   And it's critical because it can tip  
16 either way when you're trying to decide do we approve  
17 this drug or not? Because you're looking at it --  
18 well, is there clinical benefit? You may not see the  
19 full impact on the patient for 12 months or longer.  
20 It may take them that long to recover from any kind of  
21 infection state if it's that serious. So, we need to  
22 know for sure like, is there an extended period of

1 time that we measure out? So, we need to start  
2 finding these patients and talking to them, and  
3 listening to them.

4 JANE KNISELY: Thanks. I have Sara and  
5 maybe -- well, you're making your comment. Ah, thank  
6 you.

7 SARA COSGROVE: So, I wanted to circle  
8 back to Rebecca's comment about toxicity real quick  
9 with DOOR. Because the two big studies that have been  
10 done with DOOR related to toxicity have been done with  
11 Vanco and with Colistin, for which we have the luxury  
12 of 60 years of knowledge that both of those drugs are  
13 nephrotoxic.

14 And I think unless you have a signal  
15 already from a Phase I or II study, that if you're  
16 trying to do a DOOR analysis along with the  
17 registrational trial, you may be missing significant  
18 toxicity issues when you construct the DOOR. And I  
19 don't know if you've thought about those issues or how  
20 to handle it, or maybe that's a flaw that's tough to  
21 deal with and maybe DOOR is better done after, you  
22 know, the registrational trial.

1 VANCE FOWLER: Yeah, I totally agree.  
2 That's a great point. And it's one of the reasons why  
3 I feel like the ultimate contribution of DOOR, at  
4 least in the short term, will be in exploratory or  
5 secondary endpoints. I think the primary -- again,  
6 with, you know, the responsibilities that the FDA is  
7 charged with in terms of evaluating safety and  
8 efficacy -- I don't see a way around the safety  
9 component not being primary and not being evaluated  
10 independently for precisely the reasons you brought  
11 out.

12 So, I'm suggesting that DOOR Has a  
13 meaningful contribution for drugs that are already  
14 available and trials that are -- strategy trials, we  
15 can consider it as a primary. But I think for the  
16 purposes of evaluating new compounds, safety is going  
17 to have to be paramount. And, Helen, did you want to  
18 step on that?

19 HELEN BOUCHER: I would just add that  
20 by the time gets to Phase III, we usually know  
21 something about the target organs of toxicity from the  
22 preclinical and the early clinical. So, that's the

1 kind of toxicity we know we might be facing with this  
2 drug or class of drugs. Then there's that which we  
3 don't know, which Scott was talking about. And I  
4 think the DOOR, if you're going to apply it in a Phase  
5 III setting has to think about both. But the fact  
6 that you can do that is actually more than we can do  
7 in some standard trials. So, that's where there might  
8 be a benefit.

9 SCOTT EVANS: Maybe if I could just  
10 follow up. I think -- one thing -- a couple of  
11 points. One is if you use a DOOR endpoint you should  
12 analyze all the components to it. In and of  
13 themselves, they may or may not be interpretable. As  
14 I mentioned, you know, you measure duration of  
15 hospitalization, whether you can interpret that, you  
16 know, it depends on what's happening with other  
17 things.

18 I do think, though, that when you do  
19 get to late phase trials you will have an idea about  
20 toxicity. That's what the early phase trials are for.  
21 However, I do think that in the long run, the vision  
22 for a DOOR outcome, that the safety components that

1 weigh into it should not necessarily be intervention-  
2 specific.

3           So, if you're comparing two treatments,  
4 one may have a toxicity in one place and another has a  
5 toxicity in another place, the importance of a  
6 relative importance of those two things depends on  
7 their impact on patients. And so in some ways you  
8 want to be agnostic to sort of intervention-  
9 specificity. What you want is an outcome that  
10 evaluates the impact on patient lives.

11           One frustration I've always had in  
12 trials is we have all these rating systems for AEs --  
13 severity, seriousness, is it related to treatment? Is  
14 it not related to treatment? Treatment-emergent, etc.  
15 What I would like to see is a rating that says how  
16 impactful is that adverse event on the patient? And  
17 that's actually what you would like to factor in.

18           JANE KNISELY: Sue, did you have a  
19 related point?

20           SUE CAMMARATA: No. Actually, I wanted  
21 to talk about clinical trial networks.

22           JANE KNISELY: Okay.

1                   SUE CAMMARATA: But I didn't know what  
2 the time you'd want, because according to the agenda,  
3 it looks like this is wrapping up at some point here  
4 soon.

5                   JANE KNISELY: Yeah. We are well into  
6 our moderated panel discussion, I think. So, let's  
7 just go ahead and note the discussion questions. So,  
8 we talked about a lot of things this morning. DOOR  
9 was a very interesting part of that but not the only  
10 part. And so I think we should open this up now to  
11 additional discussion. So, please go ahead.

12                   SUE CAMMARATA: So, for me, I wanted to  
13 talk a little bit about the clinical trial network.  
14 Because I think on paper that always sounds fantastic  
15 in some ways. And I was actually part of the Pew  
16 meeting -- if it was out of 2016 or 2017, it just --  
17 time flies. And I recall at that meeting, and I think  
18 it still is an issue, is what is the design and intent  
19 of that trial network?

20                   If I recall, most of the pharma  
21 representatives were quite concerned about things like  
22 -- I'll say master protocols and that because of the

1 challenges of a particular drug, particular  
2 comparators, time, you know, how would you use this  
3 data?

4 I would say that I'm particularly happy  
5 to see that -- at least the Pew Trust is talking about  
6 pediatrics. I've said at that meeting and I still say  
7 it's not sexy, it's not exciting. We've talked about  
8 pediatrics. But if you want to be successful, I truly  
9 think that that is the one place<sup>3</sup> you can start to get  
10 pharma potentially involved because it's less  
11 competitive, there's less risk. It's not really a  
12 money-making area for most companies. But it's one  
13 that every single company, whether you're big or  
14 small, has to...

15 I mean, I'm currently responsible for  
16 three pediatric programs, you know. So, it's  
17 something you have to spend money -- and it might be  
18 an area of the most success, but it absolutely is not  
19 sexy to everybody else except the pediatricians in the  
20 room. But it is one area that I would highly  
21 recommend thinking about because -- for any of the  
22 trial networks.

1           But I am concerned and I'm curious in  
2 this meeting, compared to that previous meeting, about  
3 the thoughts of everybody else about master protocols.  
4 I mean, for me, a clinical trial network that might be  
5 able to be up and running, cost effective, just to get  
6 a contract signed with an academic institution in the  
7 United States can take six to nine months. And that  
8 is always one of the other challenges of being able to  
9 do trials in the U.S. So, having that available with a  
10 site that's motivated is interesting. The problem is  
11 I'm not sure there's enough volume over time to do  
12 some of these trials.

13           So, for me, I was interested in this  
14 concept of sort of the idea of the strategic trial  
15 that might not be pharma-sponsored but might be  
16 sponsored in some other way to get information to keep  
17 some of these sites open. For example, in HAP/VAP, to  
18 answer interesting clinical questions that clinicians  
19 want to have answered but then also could be a site  
20 that participates in a clinical trial since -- for  
21 example, with HAP/VAP, the guidance is fairly clear in  
22 the general construct. But a company or a sponsor



1 might want to have something different because of the  
2 nuances of their product.

3 So, I'm just curious about how other  
4 pharma companies feel about it because I see lots of  
5 discussion but I'm not sure about the reality, for  
6 example, of a master protocol type system being set up  
7 versus something that's more flexible to handle both  
8 those strategic kind of questions and then the  
9 registration type of questions.

10 JANE KNISELY: Thanks for bringing that  
11 up, Sue, because I had the same question. I also was  
12 at that 2016 meeting and heard the same thing you did.  
13 So, we heard a little bit of it yesterday from David,  
14 so I'm curious to get some perspectives from companies  
15 about what are their perspectives on these clinical  
16 trials networks? How could they be useful? Sort of  
17 this third question here. So, go ahead, Nick.

18 NICK KARTSONIS: So, thanks, Sue, for  
19 raising that. In fact, the one area of it we've  
20 talked about internally where we'd love a network was  
21 pediatrics. I mean, because I do think you've raised  
22 all the right issues around that, that I think would

1 have value in terms of that.

2 You know, I sort of harken back to our  
3 recent experience with HAP/VAP. And each of our three  
4 studies was different. And we actually talked about  
5 this. Could we have done this in the network  
6 situation? But they each looked at different  
7 endpoints and they had different visits to some  
8 extent, and just some of the inclusion-exclusion  
9 criteria also varied a little bit.

10 You know, there's a host of things we  
11 worry about around the network. You mentioned master  
12 protocols and the factors that go with that, but then  
13 there's all the operational stuff of different safety  
14 tests for different drugs, how do you handle that?  
15 Blinding, comparators, how do you handle all of that  
16 stuff? And then there's the inevitable database  
17 issue, which, every company has its own database. And  
18 I don't know how other companies are but every time I  
19 feel like we've run a database, the lights dim a  
20 little bit at Merck, then they come back on. (Laughs)

21 And so it isn't without its shares of  
22 challenges of trying to share that data across the

1 databases. So, just mention that.

2 JANE KNISELY: Maybe we can hear from  
3 Rienk and David, and then go to Chibuzor.

4 RIENK PYPSTRA: Yes. I also agree that  
5 pediatrics is a very obvious one. I think HAP/VAP is  
6 also a possibility. It all depends on the level of  
7 integration. If you have a network of independent  
8 sites, you can indeed run a common protocol and you  
9 can organize yourself, and you may have some savings  
10 on the patient numbers and therefore on cost.

11 But you could go with the integration  
12 all the way to having a common database for the whole  
13 network. And the patient data that you're collecting  
14 in a continuous fashion are immediately available in  
15 that database. And then the step of adding an  
16 investigational or an interventional arm in that  
17 becomes much more simple.

18 It also overcomes some of the issues  
19 that we had about informed consent that were discussed  
20 this morning. If you were such a site, every patient  
21 admitted to your site would enter the hospital or  
22 enter the ICU. You can determine yourself where you

1 put that barrier. And at admission, get a  
2 questionnaire. We are a research site. Would you  
3 agree to participate in research?

4 If the patient says yes, from that  
5 moment on, the data of that patient go into the  
6 database. Whether you will or not need that patient  
7 doesn't matter yet. And then when you have a specific  
8 protocol, you re-consent the patient. You are now  
9 qualifying for this intervention. Do you still agree  
10 to participate in the research? That would be  
11 something that would facilitate it.

12 And such a network would have quite a  
13 lot of advantages. First of all, it would be of a  
14 very high-quality standard. The data that you're  
15 collecting in each site would be comparable because  
16 that's how the database has been set up. You don't  
17 have different physicians collecting different types  
18 of information in their patient loads.

19 So, I think that would be a very  
20 important homogenization of the data and making sure  
21 that we can compare the data across sites.

22 DAVID MELNICK: So, I agree with much

1 of what's been said. I think -- you know, perhaps we  
2 could uncouple the idea of a trial network from a  
3 master protocol. We don't have to do the whole  
4 shebang at once, you know. And there is the obvious  
5 saving -- you know, I love this term of a single use  
6 network.

7 We reinvent the wheel with every one of  
8 these trials. This has confused me from my start in  
9 industry, you know, 25 years ago. What do you do when  
10 you start a trial? You look at the FDA guidance and  
11 at the three last trials that had been done and, you  
12 know, you write your protocol and then take it to the  
13 agency and get it approved, and you're off assembling  
14 a trial network.

15 But those frontend activities --  
16 negotiating the clinical trial agreements, you know,  
17 it's an incredibly laborious task and we pay an arm  
18 and a leg to CROs to do that work for us. I mean, it  
19 would seem to me that having a shared infrastructure  
20 that could include things like shared SOPs, you know,  
21 common CTAs, and then gradually move in the direction  
22 of, well, if there's a HAP/VAP network, we work on

1 endpoints. They're going to work and gradually move  
2 toward a master protocol that would be acceptable.  
3 So, it makes sense to me.

4 CHIBUZOR UCHEA: I totally agree with  
5 you, David. The two concepts are independent --  
6 they're complementary but independent. We really need  
7 to be focusing on the initial development of the  
8 network, and that's what we've prioritized. The use  
9 of continuous master protocol is a brilliant idea.  
10 It's one that requires -- it's much more resource-  
11 intensive. We're a bit of a way from that at the  
12 moment. It requires further development and  
13 assessment of the investability.

14 Going back to clinical trial network in  
15 general, the one that we're setting up in Southeast  
16 Asia, we really want it to be able to facilitate  
17 parallel follow-on studies but the smaller type and  
18 optimization studies. And that's one of the reasons  
19 that I'm really happy that people are talking about  
20 pediatric indications, because that's something that  
21 we see as a key area that we can achieve a lot of buy-  
22 in. We want to get away from the whole waiting ten

1 years for a product to go through and start studies in  
2 pediatric indications. And we're working with Penta  
3 to try and leverage their expertise in this area and  
4 be able to build up our network to be able to run  
5 studies like that.

6 And I'll also go to a point that Vance  
7 made earlier, which is really important, about  
8 funding. We really need to be able to try to leverage  
9 government funding for these kinds of projects.  
10 They're heavily dependent on philanthropic  
11 organizations. But the resources needed, they're  
12 really deep.

13 Another way we're setting up our  
14 network is also for our investigators to be able to go  
15 out and get their own ground funding as well. So, our  
16 secretariat function will be able to support them in  
17 proposal development.

18 And I'd like to go back to a point that  
19 was made yesterday about bureaucracy, the potential  
20 for this to be like a heavily bureaucratic way of  
21 operating. One of the key reasons we're operating  
22 with a network secretariat is it will effectively work

1 as the external business face of the network. So, it  
2 will provide a single point of entry.

3 So, the whole idea is moving away from  
4 that bureaucratic approach where you're constantly  
5 trying to find various different trial sites. It's  
6 one point of entry, and then we build from there.

7 JANE KNISELY: Okay. So, a follow-up  
8 point on this topic? Sue? Okay, go ahead.

9 SUE CAMMARATA: Well, one of the  
10 questions I did have for you around the pediatrics --  
11 and this is somewhat off topic but I'm interested to  
12 ask -- is around using those sites for drug  
13 development. Because, typically, you try to avoid  
14 going to places where you're not going to  
15 commercialize. It's just the ethics of it all. And -  
16 - but, unfortunately, with resistant bugs you have to  
17 go where you can go.

18 All the companies would love to be  
19 commercialized globally but it's not necessarily  
20 happening. So, is there some arm of that involved in  
21 this discussion that the Pew is taking about -- for  
22 products that are eventually studied? And then some



1 way to have access -- especially for the small  
2 companies that don't have partners in those areas.

3 CHIBUZOR UCHEA: In general, access is  
4 something that's really important to our organization  
5 and it is something that we're looking at. The key  
6 for us with selecting Southeast Asia as our anchor  
7 point is the access to public patient populations with  
8 hyper (indiscernible) disease and being able to look  
9 at the multidrug resistant and extensively drug  
10 resistant indications.

11 It was really refreshing to hear  
12 Steven's talk yesterday to see that this is being  
13 further explored, and that the data presented less  
14 concerns around generalized ability because that is  
15 one of the key reasons why not a lot of clinical  
16 research is done in these areas.

17 And what we're trying to do is we're  
18 trying to leverage that, we're trying to build the  
19 capacity, improve the trial site so that regulatory  
20 bodies are happy with the data. The big thing is  
21 about the value of ex-U.S. and ex-EU data. So,  
22 initially operating this trial site in this region

1 will help us to be able to leverage that and to show  
2 the potential advantages of being able to run clinical  
3 trials in these regions.

4 SUE CAMMARATA: This is actually a  
5 follow-up but it's directed more to the U.S.  
6 clinicians, because I keep hearing about the concern  
7 about not U.S. data. And I think for most of the  
8 pharma folks, and FDA, and other agencies, they're all  
9 comfortable with -- there are differences but this  
10 data is translatable.

11 And so I'm just curious because I know  
12 that there is this concern about the lack of U.S.  
13 patients. But I did a trial recently where we went  
14 out of our way and spent extra time and money to try  
15 to enroll in the U.S. and we got five patients versus  
16 860 outside the United States. And that was a  
17 significant effort. We actually delayed our timelines  
18 to try to get those U.S. patients because everybody  
19 talks about it.

20 So, I'm just curious since many of the  
21 people here actually accept that. But I keep hearing  
22 the U.S. talk about it and I'm just questioning --

1 concerned or questions about how you feel about that.  
2 Because that is where I think, for the bugs, I mean,  
3 that's where we're going to have to go.

4 VANCE FOWLER: Yeah, I mean, I'd put  
5 that on the scale of concern about -- right up there  
6 with like a meteorite hitting the planet. It's just  
7 not -- it's just not a real concern. I'd much rather  
8 have, you know, data than not data. And, okay,  
9 there's going to be practice variation. I mean, we're  
10 setting up sites and got sites going on in China and  
11 all these other places. It's definitely different.

12 But guess what? You can randomize  
13 folks there. You can block randomize. You know,  
14 there's means by which you can address that. And at  
15 the end of the day, if you're -- you know -- so, no,  
16 it's not -- to me, it's not a meaningful concern.

17 JANE KNISELY: Additional responses?

18 SUE CAMMARATA: I was just going to say  
19 the same thing. I don't think -- I actually don't  
20 even hear this as a concern brought up amongst other  
21 infectious disease doctors. I think people would much  
22 rather have data in patients with resistant organisms.

1                   HELEN BOUCHER: So, I will agree with  
2 my esteemed colleagues, but also just raise the point  
3 of view that we're in America, the most resource-rich  
4 country, and the question for us is, is it acceptable  
5 that our patients are not in these trials? And the  
6 questions are being raised by payers, and journal  
7 reviewers, and editors, and others, when there are  
8 zero or five out of 800 patients, there are -- some  
9 people think there are ethical issues.

10                   So, I would just submit that it's at  
11 least worth of our consideration before we say, well,  
12 we're just going to give up on this enterprise in  
13 America.

14                   VANCE FOWLER: I'm pretty read to give  
15 up. I mean, I think I'd much rather -- I'd much  
16 rather go ahead and get -- actually try to get some  
17 trials done and get some answers and some data  
18 somewhere. I know, I get banged around about the  
19 journalizability and all the ex-U.S., yadda-yadda, but  
20 for crying out loud, if we weren't in a crises, we  
21 wouldn't all be sitting here and investing two days of  
22 our time on this issue. And that's from all sides. I

1 think -- we're in a crisis, folks. The building's on  
2 fire, you know, and we need to do something. We need  
3 to get some data, we need to understand how to treat  
4 patients, do the right thing. Crawl, walk, run, fly.  
5 Thank you.

6 JANE KNISELY: John looks like he has a  
7 burning response. Pam's had her card up forever, so  
8 we'll go to her after John. And then I think we do  
9 want to give the audience an opportunity to ask some  
10 questions. So, if you have one, please come to the  
11 microphone and we'll continue to work here in the  
12 meantime. So, go ahead, John.

13 JOHN REX: So, Helen, are you concerned  
14 that we're in a position of looking like we're using  
15 the rest of the world as our guinea pig? I mean, is  
16 that sort of the idea you're getting at, that we need  
17 to be sensitive to that notion?

18 HELEN BOUCHER: I think that's part of  
19 the issue, and I think it's also the question of  
20 whether our patients deserve the chance to be included  
21 in these trials. And what we're seeing is that  
22 they're not.

1           So, I totally hear Vance and Sara and  
2 the need to get on with it, and we cannot let the  
3 perfect be the enemy of the good.

4           LINDSEY BADEN: But there are multiple  
5 problems to be solved here. I mean, we need high  
6 quality data, full stop. I agree with Helen. It's a  
7 -- it's a shame that that can't also occur in the  
8 Americas. But I don't think they're exclusive. On  
9 the other hand, we need high quality data more  
10 quickly.

11           JANE KNISELY: Okay, Pam. Sorry.

12           PAMELA TENAERTS: I'm actually not a  
13 patient person but... That's actually the point I  
14 wanted to make. So, with City, we started this effort  
15 in antibacterial work. A lot of the comments I got  
16 from people in the field was, well, we've been talking  
17 about this for ten years. What is going to be  
18 different about this time?

19           May I remind you that that was in 2012?  
20 And it feels like we're still having the same  
21 discussions over here. So, what I would like to say  
22 is, you know, we are underestimating the risk of what

1 we're doing right now and overestimating the risk of  
2 novel approaches. And I really would like you guys  
3 and girls -- because I've been told that you can't  
4 really say "you guys" because it's discriminatory --  
5 that all of you sort of have an open mind. And when  
6 people have new ideas, to test those ideas. Make  
7 funds available. And I'm looking at the NIH because I  
8 don't know where else the money's going to come from.  
9 But to test those opportunities for new ideas.  
10 Because to just go off and do new things -- new isn't  
11 always better. Because if we thought everything was  
12 going to work then why are we even doing the clinical  
13 trials to begin with? Because everybody is convinced  
14 their drug is going to work when they go into  
15 development, right? Otherwise you wouldn't do it.  
16 But we've been proven wrong.

17 No reason to think that some of these  
18 things that we think are going to work to make this  
19 better may be wrong too and have unintended  
20 consequences. But I would like to say, like, just  
21 keep an open mind and start doing something. Maybe  
22 just start, and that'll change things.

1 I mean, you guys have come a long way,  
2 because when I talked about master protocols in maybe  
3 2014, I heard, oh, that doesn't work in our field.  
4 So, I'm not saying -- but there's other things. Beg,  
5 borrow, and steal from other specialties. I mean, you  
6 know -- I don't know, that's just what I would like to  
7 say.

8 I think what we find the most difficult  
9 with the work we're doing is coming up with  
10 recommendations -- as people, you know, go back to the  
11 status quo, it's easier to sort of do what you're  
12 always doing than do something new. So, anyway...

13 JANE KNISELY: Roger, you've also had  
14 yours up for a while.

15 ROGER LEWIS: So, I wanted to make two  
16 comments about the issue of out of U.S. data and  
17 applied to U.S. patients. The first is just a request  
18 for statistical clarity when we're discussing the  
19 differences. There is a tendency, at least in  
20 informal conversation, to confuse differences in the  
21 overall average outcome of patients in different  
22 locations from the expectation of the treatment of



1 fact.

2                   And the thing that is scary in terms of  
3 the use of out of U.S. data to inform U.S. regulatory  
4 decision making is if you think the treatment effect  
5 is heterogeneous as opposed to the background success  
6 rate of disease. And I just urge us when we discuss  
7 this, regardless of the position we're taking on it,  
8 that we're very clear to make a distinction between  
9 differences in prognosis and differences in efficacy.

10                   The second point I would make is that -  
11 - and I think Helen was also referring to the Belmont  
12 Report principle of justice, that the population in  
13 whom the risks of research are borne should be the  
14 population that benefits from the results of that  
15 research. I didn't say it very well but it's in  
16 print.

17                   That can -- ideally, there's a one-to-  
18 one correspondence between the population on which the  
19 experiment is conducted and those who benefit. But  
20 you can -- when that is infeasible, you can partially  
21 address the inequity by making sure that the benefit  
22 of the research is made available to the population in

1 which the research is conducted.

2           So, I don't want to -- I'm not in a  
3 position to comment on the feasibility of doing these  
4 studies in the U.S., and if doing so delays the  
5 availability of the agents globally, that's an  
6 important negative aspect for everybody. But we  
7 should address the question of whether these agents  
8 that are being developed are then available in the  
9 countries in which the research is conducted.

10           RYAN CIRZ: I'll be brief because that  
11 was essentially what my point was, was hearing...  
12 Well, I guess, first worrying about ex-U.S. predicting  
13 U.S. I mean, we do use mice to set our dose initially,  
14 if that makes you more comfortable. And, generally,  
15 if you are really rigorous, you get it right every  
16 time. We don't see a lot of failures except for sort  
17 of dosing errors that a lot of people think could've  
18 been predicted.

19           But that is a worry, and I think about  
20 this a lot. And regardless of whatever you thought  
21 about the plazomicin study, we did most of it in  
22 Greece and the drug has not been back to Greece in

1 years. And whether you believed it had that effect or  
2 not, those patients don't have access to it. And that  
3 is what's going to happen. And there is that little  
4 bit of risk of saying, let's go study it over there  
5 where we don't have a lot of it. Let's go study it  
6 over there and then we'll bring it back here to  
7 protect ourselves. And I think someday we've got to  
8 be prepared for how to handle that properly.

9 DAN RUBIN: All right, so we have  
10 another online question. Roger, this is a follow-up,  
11 I believe, from the earlier John Tamico question about  
12 borrowing. And remember, the earlier question was  
13 about CIAI, and the follow-up is that "The issue is  
14 not just a difference in treatment effects but in  
15 noise from source control and anticipated small  
16 numbers of patients at each body site. So, it is a  
17 body site issue, not an antibiotic site issue. Should  
18 this disqualify CIAI?"

19 ROGER LEWIS: Great, thank you. So,  
20 the hierarchical model takes into account the signal  
21 to noise ratio within each of the sites or the  
22 subgroups. The signal to noise ratio is influenced

1 both by, obviously, the number of observations you  
2 have within that group and also the variability you  
3 see.

4           So, if there's a source of nonbiased  
5 noise, just randomness in the adequacy of surgical  
6 site control or ancillary therapy, that can be handled  
7 pretty well within the model. If what's happening is  
8 the source of noise systematically makes a drug  
9 ineffective or, I guess, conversely, more effective --  
10 but ineffective in a site, then that's an issue  
11 because then the site really isn't exchangeable. You  
12 know something's different about that site than the  
13 other sites.

14           And, statistically, it's completely  
15 analogous to a setting in which you know the drug  
16 doesn't get there. If you knew the drug doesn't  
17 penetrate the meninges even when they're inflamed, it  
18 shouldn't include meningitis as one of the infection  
19 types in a hierarchical model because you know it's  
20 different.

21           So, this is -- there was a brief  
22 comment in my presentation where I said that the

1 decision to include a site, or it could be a disease  
2 type, in a hierarchical model should be based on pre -  
3 - in learn phase or earlier data that shows that it's  
4 reasonable to think of this collection of diseases as  
5 potentially ones that would respond homogeneously to  
6 the treatment effect. If you know something's  
7 different and you're asking a separate question and  
8 you shouldn't be including them in the model.

9 DAN RUBIN: All right, I think that's  
10 going to close our moderated discussion. So, thank  
11 you, everyone, for making this a great event. And our  
12 next item on the schedule is Dr. John Rex is going to  
13 provide a summary.

14 JOHN REX: So, let me first say that  
15 this has been a really instructive day and a half.  
16 And Sumathi and I put our heads together and thought  
17 about the stuff we've learned the last day and a half  
18 and where it might go. And I'm nominated to talk  
19 about it, but this is really a group work product.  
20 So, all of you are here as well.

21 So, these are the big messages we're  
22 going to cover: AMR Enterprise in crisis. We can't

1 fix it all today but some things we can. What are the  
2 emerging ideas? What do we do next? And so, the fact  
3 that the AMR Enterprise is in crisis, that the Check  
4 Engine light is flashing was nicely demonstrated by  
5 several of the talks.

6 Late stage commercial failures have  
7 occurred and seem likely to continue. And even when  
8 successful, your stock gets shorted and your NPV goes  
9 down, and the return is less than that of even a  
10 moderately successful oncology product.

11 So, what are the elements that are  
12 within our grasp? And this was really -- I learned  
13 some things very helpful here. So, we know that push  
14 funding works, actually. CARB-X, BARDA, NIAD,  
15 Wellcome Trust, Novo REPAIR. They have lit a bonfire  
16 in the preclinical space, and there are some neat  
17 things coming. Can the science problem be solved?  
18 Can we find new antibiotics? I think the answer is  
19 yeah. It looks like we're going to.

20 We've also learned that we can reliably  
21 get products to approval -- many products to approval,  
22 with basic studies in well-understood infections. And

1 helpfully, these studies generalize reasonably well to  
2 the U.S. We just had a good conversation about that.  
3 Some more detail could be added here.

4 But, importantly, we can't generate the  
5 same quality of data for all uses. And other possible  
6 uses of a new drug are always going to exist and are  
7 important to clinicians. Five o'clock this afternoon  
8 you may have to treat a patient who's never going to  
9 have a labeled drug for their meningitis. And they're  
10 -- just pick any one of those things. There's nothing  
11 labeled for it so what do you do?

12 So, this flips around to what do we  
13 want? And broken down here, it's by important  
14 stakeholder group. So, physicians and ID physicians  
15 want access to all of the data, preferably interpreted  
16 for them in some way. Payers and P&T committees would  
17 like that same thing but they'd like a measure of the  
18 quality of the data. Patients would like us to hear  
19 their voice and think about how they feel net of the  
20 whole process.

21 And companies would like validated and  
22 acceptable mechanisms for promoting based on the data

1 on resistant pathogens and difficult infections. You  
2 know, we get it -- the CUTI's not where you want to  
3 wind up but it's hard to generate the rest of it. And  
4 FDA had to label per regulation. And remember the  
5 phrase, adequate and well-controlled.

6 So, two slides with ideas. The first  
7 one is -- the broad title here is Tell the Story.  
8 Theme A: Make clear to ourselves and our peers the  
9 limits on data generation. Everybody needs to  
10 understand what you can do, what you can't do. It's  
11 very easy to wish for me, especially when you've never  
12 -- you can't feel the complexity of producing the  
13 information. And if there's a better way to generate  
14 this data we would be doing it. We've searched long  
15 and far to find ways to generate the data and we are  
16 constrained.

17 We as a community also have to be very  
18 clear on the limits on the product label. And without  
19 rules, we would have the Wild West, arbitrary decision  
20 making. And the role of the FDA is to consistent --  
21 one of their many roles is to consistently apply the  
22 rules so that we know what's coming. And the standard



1 of that is well-controlled, and that's the standard.  
2 Work with that.

3 But there is something else that I  
4 hadn't anticipated was going to come out of this, and  
5 this was this idea of sharing the other available  
6 data. Keeping in mind the limits on the label, we get  
7 the data published -- we should talk about the nuances  
8 of the trial. But there's something else that I think  
9 we could be looking for, and that is a sort of peer-  
10 to-peer communication. We're nominating IDSA here to  
11 the society for validating -- you can validate by  
12 publishing an informed critique of the available  
13 secondary data.

14 And I do mean this as peer-to-peer.  
15 It's 4 o'clock, I'm stuck with this patient, I might  
16 send my fellow to the library. He or she might find  
17 the right information. It's actually better if Helene  
18 spent some time six months ago reviewing it and she  
19 wrote down what she thought she would do in this  
20 unusual circumstance. It's the information that you  
21 would like to have.

22 And reviews like that can be used for a

1 number of things. They can be used by a company for  
2 discussion with payers. If written correctly, it's  
3 also the thing that when you want to use something  
4 off-label you can show to the insurer to say, shut up  
5 and just pay for it. That's what's in this document.  
6 Write it down in advance. And it might be usable for  
7 promotion. I'm not sure about that or not. We also  
8 need to include Europe in this conversation. So, this  
9 is all about telling the story.

10           The other part is Use the Data. Theme  
11 A: Be Clear on the Power of the Standard Indication.  
12 Modern non-inferiority sites are powerful tools. They  
13 do detect inferior agents, so it's an interesting  
14 presentation from Aaron about how few it takes to find  
15 the dog, you know? You're going to know pretty  
16 quickly if it's no good. They provide clear safety  
17 and efficacy comparisons, they facilitate initial  
18 approval, and they provide the basis, the launch pad  
19 to get you to the other stuff. And then better use of  
20 the data we already have.

21           A bunch of neat ideas here that are  
22 going to take some thinking. How do we borrow data

1 across indications? Could it be that we use different  
2 thresholds for different settings in terms of the data  
3 that we're willing to validate? And don't forget  
4 about the idea of (indiscernible) patient-oriented  
5 measures. And I'm going to add DOOR. It didn't get  
6 typed in here in time. But that's the idea that we  
7 should be working with.

8                   And then, finally, generate the data  
9 more efficiently. I've heard some nice discussions  
10 about that. It's not a panacea. Platform trials show  
11 a potential to reduce cost and speed data generation.  
12 The idea that the sites would already have a contract  
13 in place. That right there saves a year in getting  
14 the trial actually running.

15                   And the trial platform thing seems  
16 particularly true after initial approval is achieved.  
17 Studies in pediatrics, HAP/VAP, and rare infections  
18 would be especially suitable here. That was a theme  
19 that we heard when developing the concepts that you've  
20 heard about for the master protocols.

21                   So, it's the last slide. Great  
22 conversation. And I want to give a shout out to

1 Sunita Shukla, who is sitting right there and was the  
2 ringmaster for making this meeting happen. Well done.  
3 Thank you very much for your help with that.

4 (Applause)

5 She had a bunch of people to chase down  
6 and she made it happen. Nothing is set in stone as to  
7 what's going to happen next but a subsequent debate  
8 seems needed on particularly the three topics listed  
9 here: How do we borrow data across indications? The  
10 idea of different thresholds for different settings --  
11 what is adequate and well? And how do we include  
12 Europe in this conversation?

13 And I think if we start working --  
14 those are things we can work on, in addition to the  
15 things the societies can work on, and I'm hopeful that  
16 we will have a next conversation. So, thank you to  
17 FDA, thank you to IDSA, thank you to Pew, thank you to  
18 the NIH for convening this session. Safe travels.

19 (Applause)

20 JOHN FARLEY: And I think I speak for  
21 all of us in the Department of Health and Human  
22 Services that have been part of this, that we have

1 gotten a lot of very useful input and ideas. And I  
2 also want to thank IDSA, and Pew, and NIH for co-  
3 sponsoring this event. We're committed to support  
4 some of the efforts that will come out of this meeting  
5 and we're also committed to reconvening this group at  
6 an appropriate time in the future because we think  
7 this was a really useful meeting. So, thank you.

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