Everything is a risk of benefit or cost of benefit. So in this content we ask ourself how do you quantity resistance over time for your comparative? There's a piece actually missing in this so called NI trials in the design in the final analysis, even evaluating the new agent.

Now the third one is also very important. If you look at a trial you maybe have a different type of infections in your patient. So you have a third bucket and you figure out what kind of type of infections also very important. Now, today we cannot have a conversation based on this so called resistance because we don't have very good information. Lets just take a very simple idea, using what everyone's doing right now, asking ourself how much we should give up and figure out NI margin based on placebo rate. Next one, please.

Now let's think about it when you design a trial. And suppose you started with a three bucket, the severe case, a serious case, not a serious case. Supposing the design state you want one-third patient belongs to severe and etcetera, one-third, one-third. And supposedly your placebo rate -- I (inaudible) this word liberal means you usually use a upper bound or whatever you want to call 95 percent and 40 percent cure rate, 55 percent and 80 percent. So you will notice when

 

Dr. Spellberg speaks those numbers are very close to what he got in his presentation. And supposedly my active control I used a conservative number. For example this lower bound of a 95 percent confidence, you know, this is 80 percent 85 90 so conventionally we just take the difference between 80 and 40 percent efficacy retention. Why do you want to use 50 percent? I don't know, but that's convention. All right, 85 minus the 55 divided by two is 15 etcetera. In this trial you just -- because one-third, one-third and one-third, you average those guys up you got a .1. Now you got a .1, you talk to FDA friends and say, "Look I want to have a 1 percent, this is justification." They say, "Fine lets go ahead and do this trial." Next please.

Now we can use this NI margin which is very important to us because you try to figure how many observation in each arm and figure out do you have enough information towards the end of the trial. And you have a statistical analysis plan whatever it is in the design stage. Next one please.

Now, of course, the -- realistically speaking in real life everybody knows, again better than I do, even if we have planned one-third, one-third, one-third we won't get a one-third sometimes. So I would recommend people closely matching the

 

plan proportion of subject in each bucket. If in the interim look which is not really regular interim analysis, suppose the total proportion of this -- in a bucket of patients cannot be attained, you probably should readjust your sample size and readjust your weighed average of NI margin instead of using the original one. And in the past two years our group developed a very nice package, how do you actually use a prediction idea to assess the feasibility, futility during the interim look. And we can use this device to figure out if your non-inferiority actually is not non-attainable or is attainable. Next one please.

Now in the final analysis I would suggest that don't use a the original .1, for example. For example, we should have used observed a proposition of patients in each bucket before unblinding the responses, then we adjust NI margin for the final analysis, instead of always use the 1 percent that's the water under the bridge. Next one please.

Now let me just give you one very simple example demonstrate we should not always use one single number for everyone. This is actually for three different types severity of infections. And we have four different studies. The only difference, I'm going to use Professor Spellberg's number 21

 

percent NI margin, 14 percent and 7 percent that's what -- from his presentation already published.

Now this study, Steven's (ph) study in year 2000, and you notice there's a percentage of 11.5 percent of people belongs to this bucket. And 21 times the number 11.5, that's 2.4 percent and you had 14 percent times 44 percent. This is a conversation of your patient in this study and you got 6. and etcetera. You add it up averaging, it's 12 percent and that's your NI margin, But if you notice the next one we have a different composition, 6.4 percent belongs to this bucket. We don't have any patients in this bucket, we have 6.6 percent in this bucket. You use a weighted average you got 16 percent. So the point I would like to emphasize, next please, is this number, NI margin, actually is varied from your comparative. comparator's response rate. We just used the same response rate same placebo the only thing I changed is the composition of your patient in each study. Even that piece you notice that the NI margin varied from study to study.

Next one please. So what's the future? I think this retention efficacy in different scenario are important, for example we should have more data in this part. So what is it really talking about? How do you quantify this resistance? And

 

the second part is also very important, accounting for the mix of the box. And the third one is very important. I was told that Professor Fleming's really worried about how you choose the comparative. If you choose the, you know, the lowest cure rate everyone can get into the picture. I don't know how true it is, Tom, forgive me, if I quoted wrongly. The next one, please.

So I left this quote in with Winston Churchill back in 1942. I would like to say this actually is the beginning of our conversation. I hope we can have a three-way dialogue among industry and FDA and academic world. Thank you very much.

BARTH RELLER: Thank you, Dr. Wei. Our next presentation will be Dr. Brad Spellberg on the behalf of the IDSA.

BRAD SPELLBERG: Okay. Thank you very much. I have a lot of material to go through and a very short time to get through it. So I'm going to be moving fairly quickly to preserve time at the end for discussion. And I want to start by pointing out that the materials I'm about to present were compiled by members of the anti-microbial task test of the IDSA and that no member of the task force received any financial support for this work.

We all know why we are here, it's been discussed this morning. The real problem that we have is that antibiotics

 

became available in an era prior to the widespread use of placebo controlled trials so, we have an imperfect understanding of the magnitude of efficacy of antibiotics for a variety of types of infection. And what we really need to enable us to better understand non-inferiority margins is a method that would allow us to estimate in some form robust manner the antibiotic effect side for disease that does not have placebo controlled trials available. And that's what we really set out to try to accomplish.

We focused on cSSSI because of its large public health impact because current antibiotics for cSSSI all have unique limitations and because the advisory committee and the FDA are going to have review drugs for this indication and it's going to be very difficult to do that without a clear understanding of the magnitude of efficacy of antibiotics for these infections. So we conducted a systematic review of the literature we used the search engines as shown, we used these search terms. I'm not going to go through them individually. We did focus on the years 1900 to 1950 so that we could estimate what the cure rates for these infections were in the pre-antibiotic era and in the immediate post-antibiotic era through the period where penicillin retained activity against most strains of staph with

 

resistance really becoming widespread in the 1950s.

Now we spent a lot of time this morning talking about what an end point would be, what cure is. As you can imagine an article spanning 50 years of literature, the definition of cure works ordinarily disparate. We did not find it reasonable or rational to look at cessation of worsening of the infection. So what we tried to do was to cull out various other types of definitions that would define failure, from all the manuscripts, and then go back and look at all the manuscripts with the same criteria for failure. We call defined cure as the patient being alive and not having any of these specific complications which I think anyone would look at and say, "Yes and if you have these things that means you fail."

And in order for the manuscript to be included in our calculations of cure the manuscript had to describe at least one of these other criteria in addition to life or death. If it just described survival we included in the calculations of mortality but did not include it in the calculations of cure. We calculated weighted average cure rates and 95 percent confidence intervals for patients being treated with antibiotics and non-antibiotics and then used a very conservative definition of lower bound antibiotic effectiveness. We subtracted the

 

upper bound estimate of cure without antibiotics without antibiotics from the lower bound estimate of cure with antibiotics.

Now the full manuscript resulting from this work was provided to the FDA and has been posted publically. Because time is short I'm not going to be able to go through all the data in that manuscripts but certainly happy to discuss more elements in the Q and A session. We did do estimates of publication bias by heterogeneity which I'm not going to have time to go into. And perhaps most importantly I'm not going to discuss today at all, the sulfonamide data, which we do go through extensively in the manuscript. And the reason -- even though this was a primary arm of the FDA briefing document the reason I'm not going to discuss the sulfonamide document is because monotherapy sulfonamides are irrelevant to modern medicine and they have been irrelevant to medicine for over 40 years ever since dihydrofolate reductase inhibitors came along. And we know that when we combine trimethroprim or other DHFR inhibitors with PABA analogues you get synthergy in vitro and a marked improvement in efficacy in vivo. So that -- and consistent with the historical experience in all of our analyses as shown in the manuscript, penicillin was clearly superior to

 

sulfonamides.

Now we found 90 peer review publications spanning that 50 year period that were included in our calculations describing outcomes in more than 28,000 patients with cSSSI. So this is a very robust data set from which to cull analyses. We also found two other studies that were not included in our calculations but which are very important to provide context for the efficacy of antibiotics. The first study was a review published from Cook County Medical Center looking at the mortality rate of erysipelas on an annual basis over a ten year period. And there are two important features that come out of the study. The shockingly high in the pre-antibiotics era, 12 to 16 percent on an annual basis. And at the very year that sulfonamides became available there was a sudden massive decline in mortality.

Now similarly investigators on an entirely different continent used data from the Norway National Death Registry looking at the annual mortality rate erysipelas over a 50 plus year period starting in the 1880s and you can see that that mortality rate was fairly similar, year after year after year for more than half a century, until all of a sudden sulfonamides became available and there was an immediate massive decline in depth and you can see here this is a log scale. Mortality

 

stayed the same for a few years and then World War II ended and penicillin use became widespread and another massive reduction in mortality down to levels that frankly are very similar to what you would expect even in the modern era. And so the mortality rate of these infections in the pre-antibiotic era was quiet substantial, generally has been underappreciated because as Dr. Corey pointed out before, the efficacy of these antibiotics are so substantial for these infections. Now in terms of our quantity cure estimates looking at 37 studies describing cellulitis and erysipelas, most of these studies did not describe microbiology, but of the few that did, are consistent with what you would expect in the modern era when you're talking erysipelas or you're talking cellulitis in the absence of a collection of pus. The predominate organism was beta-hemolytic strep and staph auerus was number two.

When we looked at cure rates with a variety of non-antibiotic regiments as shown here, we did not find differences in cure rates across these treatments. And so we lumped all of these non-antibiotics treatments into one group that we call, non-antibiotics. And when you calculated weighted average cure rates we found that the cure rate of a non-antibiotics regiment for these infections was 66 percent

 

point estimate with a confidence interval shown here that the penicillin cure rate of 98 percent with the confidence interval shown here. So the point estimate of effect size of penicillin here was 32 percent. And when when you calculated the lower limit an estimate of the lower limit of effect, by subtracting the upper bound estimate from non-antibiotics from the lower bound estimate of antibiotics you come up with a 28 percent cure rate estimate for cellulitis erysipelas. I want to point out that this is cure rate with systemic penicillin.

Now I'm not going to show the data for cellulitis/erysipelas, but I will for the other two disease entities. When you look at the topical or local penicillin the cure rates are far less then the cure rates for systemic therapy. And, of course in the FDA data that was presented earlier, the penicillin data that for shown was for topical and we need to be talking about systemic penicillin therapy when we're talking about the cure rates. When we're talking about mortality from 52 studies describing more than 23,000 patients with cellulitis/erysipelas, the mortality rate of all comers for this disease was 11 percent but with a very tight confidence far lower and again was probably comparable to what you would expect in the modern era.

 

Now moving on to wounds or ulcers we looked at traumatic surgical and combat wound or ulcer infections. Microbiologically most of these studies did describe results and again, totally consistent with the modern era. Staph aureus was number one, beta-hemolytic strep was number two, there was some alpha strep and there were rarer cases of polymicrobial infections. Again, completely consistent with what you would expect in the modern era.

Now I also want to point out that in contrast to the cellulitis data for wound or ulcers it was very difficult for many studies, for most of the studies to differentiate who got systemic penicillin, topical penicillin, local penicillin and in fact there were patients in these studies that got mixtures. And in the primary analysis what we did was simply lumped all those patients together and then we did a sensitivity analysis just looking at parenteral therapy. The cure rates for wound/ulcer infections were extremely low in the pre-antibiotic era and there was a substantial effect of penicillin in improving these cure rates. And in fact the authors of many of these studies point out that these cure rates are actually underestimates. And the reason is that the way that non-antibiotic therapy was administered for wounds or ulcers was

 

extensive debridement and then prolonged healing by secondary intention. And so you're talking about months of hospitalization in which other complications could occur and that's because you simply could not oppose the edges of a wound that was infected.

Now when penicillin came along it was quickly realized that you could often oppose the edges of a wound, stitch the wound closed and give penicillin and still cure the infection and your therefore talking about cure rates that are much faster. But it's also a much higher barrier for achieving cure because you've opposed the edges of the wound in addition to giving the antibiotic. So this is really an underestimate of the true effect of the drugs for these diseases. And the lower bound estimate of cure here is 42 percent for penicillin. Again, this is for patients receiving mixtures of topical, local and systemic therapy. When you look just at the seven studies it clearly describe cure rates for systemic penicillin and not for topical or local, you find a higher cure rate 89 percent compared to the 83 percent in the blended analysis I just showed you. Of course the confidence interval is wider because there are much smaller number of patients here. Nevertheless if you used the systemic penicillin data here the lower limit of

 

antibiotic effectiveness is 44 percent. We chose to stick with the 42 percent number from the blended analysis because it was more conservative. We really wanted to go out of our way to try to be as conservative as possible on these calculations. So when we talk about, at the end, our analysis of cure we're going to stick with the 42 percent number, not the 44 percent number.

Now for major abscesses again almost all of these studies era. Almost all of these infections were caused by staph aureus. These were truly complicated abscesses. We excluded furuncles from the analysis. These were carbuncles or major abscesses. In data that I'm not going to show you, but is in the manuscript, the mortality rate in the non-antibiotic arm for major abscesses was six percent, so these were truly complicated infections. Nevertheless, I&D does have effect and so the cure rate without antibiotics for these infections is higher than for the other two diseases. But I want to point out that this cure rate is quiet -- is substantially lower than what you would expect for an I&D of a furuncle or a simple boil, where we have reasonable data that would suggest that cure rate that should be on the order of 85 - 90 percent. So it's substantially lower because these are more complicated infections. I want to reiterate the point that Dr. Corey made earlier, Chip Chambers's

 

study looking at keflex versus placebo for uncomplicated abscesses was a dual placebo study because the majority of patients in that study were infected with MRSA against which keflex has no activity. You cannot use that data set to estimate the antibiotic efficacy of these infections, but you can use it to estimate what the placebo cure rate is. And so again, the cure rate here without antibiotic therapy is lower than what you would expect because these infections are more severe. Penicillin had a clear efficacy in these infections here. You can see that our lower bound of efficacy is 14 percent. Now in contrast to systemic penicillin all the data I just showed you was for systemic penicillin, when we looked at several studies that looked at topical or local penicillin for these infections, the cure rate was much lower and in fact was not statistically different than the cure rate with non-antibiotic therapy. Now the importance of this is if penicillin was marginally effective or placebo it would not matter what route of administration you would it. But in fact it does matter. You have to give the antibiotic by the effective parenteral route to get the efficacy of the drug. These data have been mentioned there was a recent in the modern era Phase 2 dalbavancin dose escalation study looking at

 

patients randomized to receive one or two doses of infection, and the cure rate in the two dose arm was 30 percent better than the cure rate in the one dose arm. Presumably the cure rate in the one dose arm was better than what you would get with a placebo so this is really a lower bound estimate of what you would expect the antibiotic efficacy is. And the importance of this data, despite the fact that this was a relatively small study, is that the cure rate estimate from the study turns out to strikingly similar to the cure estimates we derived from historical analysis, as I'll talk about in a minute.

The bottom line is that we found unambiguous, robust evidence of a large antibiotic treatment effect for complicated skin and skin structure infections with lower bound estimates of antibiotic efficacy compared to non-antibiotics of 28 percent for cellulitis erysipelas, 42 percent for wound ulcers and 14 percent for major abscesses. Now this -- a little bit of my Thank you, Dr. Wei and the Arpida team. What we're saying here is that the implications of these results is not just in the planning of future non-inferiority studies, but the interpretation of non-inferiority studies that have been completed. You can -- the overall effect size of antibiotics for a study is going to depend on what proportion of patients

 

enrolled in that study have the subsets of cSSSI that we've talked about, cellulitis erysipelas, wound ulcer, or abscess. And you can use this formula to calculate a precise estimate of what the antibiotic effect size should be for that study. You simply multiply the portion of patients enrolled in the study times the cure rates that we've just described for these infections. And as Dr. Wei has pointed out, if one-third of the patients enrolled had cellulitis erysipelas, one-third wound ulcer and one-third abscess, that is if they were evenly distributed, the cure, the effect size of that study would be 28 percent. If more than one-third of the patients enrolled have wound ulcer infections the effect size would be proportionately larger. And if more than a third of the patients enrolled had abscesses the effect size would be proportionately smaller.

Now I want to spend a few minutes talking about this. Okay. If the goal, and I emphasize "IF", if the goal in setting a margin is to preserve 50 percent of the effect size and you have a 28 percent effect size in the study that means the non-inferiority margin for that study should be 14 percent. Now, we are not advocating preservation of 50 percent of the effects size for this disease. We actually think that this is conservative, that is you can make a rational argument for

 

preserving less than 50 percent of the effects size. Because what we're talking about here is cure, the mortality rate is very low even with relatively ineffective antibiotics like sulfonamides, the mortality rate is very low. We want to point out the preservation of 50 percent of the effect size is completely arbitrary, but that's not mentioned in any specific guidance document even though it's often discussed.

So, for a disease that has a low mortality where you're looking at clinical cure it may be reasonable, depending upon the drug if it has specific advantages over other drugs, to preserve less than 50 percent of the effect size. We also want to emphasize there are also other statistical methods that are around, floating around, that may allow one to more rationally derive what M2 should be from M1 and that we hope that there is discussion in the future about the potential use of these statistical methods to make a more accurate and more rational choice for what the margin should be based upon what the effect size is found to be. So there's plenty of evidence of robustness of our analysis. There were time to cure studies that we mentioned in the manuscript that I don't have time to go through today, some of which were described during the FDA presentation. Many of them were controlled studies, antibiotics

 

versus non-antibiotics. Every single one of them showed a remarkable superiority of antibiotics compared to non-antibiotics. We've shown that topical antibiotics are much minimally effective drugs. 1 If they were minimally effective it wouldn't matter what route of administration you gave them by. We've showed that the modern dose escalation study of dalbavancin provided an estimate of antibiotic efficacy that was strikingly similar to our estimate derived from historical data sets and in fact there have been several other manners of calculating the effect size, presented by the sponsors, which also derive a 30 percent effect size. And we have data that we didn't present but that the FDA brought forth from placebo controlled trials of impetigo again suggesting a 30 percent effect size as before. So we have multiple independent means, multiple independent processes, done by multiple independent groups all converging around an estimate of antibiotic efficacy of about 30 percent compared to non-antibiotics for cSSSI.

Finally, we have population based study that show a massive mortality benefit of antibiotics for these infections. And I want to spend a moment delving a little bit deeper into this issue. We've heard comments made that the mortality rate of erysipelas could be as high as 50 percent in the right age

 

groups, but basically all comers was 11 percent. This is a shockingly high mortality rate for these infections. We don't see mortality rates anything close to that in the modern era because we have antibiotics. So let's look at a modern randomize placebo controlled trial of myocardial infarction that was published 20 years ago in Lancet. This was a multi-center international study of patients with a MI, randomized, received placebo, aspirin or streptokinase. And the mortality rate from myocardial infarction was 12 percent in the placebo arm, very similar to the mortality rate we're talking about in cellulitis erysipelas in the pre-antibiotic era.

The mortality benefits of antibiotics, reducing mortality less than one percent is far greater than the mortality benefit of aspirin or streptokinase for myocardial infarction in the modern era. The number needed to treat to save a life is far small.

We have forgotten how deadly these infections used because we have antibiotics that treat these infections. I want to underscore the fact that mortality is important as evidence of robustness of our analysis, but because the mortality rate with antibiotics is so low, mortality by itself is not a viable end point for these infections or for these studies. We've

 

shown evidence of historical evidence of sensitivity to drug effect. Do we have evidence of assumptions? The microbiology is very similar, as the FDA did a nice job of pointing out, and as we reiterate in the historical studies in the modern era we have modern data sets that do suggest that the efficacy we found in historical studies is very similar to what we see in the modern era. The mortality rates in patients treated with antibiotics in historical studies are very similar to the mortality rates in modern studies. So we do believe there is evidence of consistency.

Now what's the limitation? Okay. The biggest limitation obviously unequivalently is that our analysis rely very heavily going to be able to do get around that problem. We did as thorough a literature review as we think could have been done. There were no other data available. Nor will better data be coming, because the efficacy of antibiotics -- if nothing else in terms of reducing mortality for complicated skin infections precludes the use of the placebo controlled studies for these infections. And frankly, even if you weren't concerned about the ethics of it the studies are not enrollable. Physicians, patients and IRD's will not allow you to put patients with complicated skin and soft tissue infections into a placebo

 

controlled trial. We're not talking about uncomplicated skin soft tissue infections.

So what we have is a large data set that has evidence of robustness that multiple independent means of trying to figure out what the antibiotic efficacy is all converge on a similar number, but that it's imperfect. We have imperfect data, equivalently. I think we need to remember the words of Voltaire "The perfect is the enemy of the good." We have all the data that we've going to have. We need to make a decision based upon the data that are available acknowledging that they are imperfect. And we need to weigh those imperfections against the critical need to get new antibiotics on the market. We really are in a crisis mode in antibiotic development here. This curve needs to start going in the other direction and we need to weigh the limitations of the available data sets against the public health need to turn this curve around. We have to remember that antibiotics are truly a unique drugs. There are drugs in no other class that loose efficacy in transmissible manner over time. No other class. This means there is a unique public health need to continually be making new antibiotics available to deal with resistance which is constantly catching up with the antibiotics already on the market. That unique public health

 

need is not true of drugs in any other class. And again we must factor in the unique public health need when we're weighing the limitations of the data.

I want to close with a brief anecdote to remind us both of how bad things were and how much better they got very quickly when antibiotics became available. So, I'm going to take you back to 1942. A four-year-old girl in excellent health suddenly developed a severe facial cellulitis that spread relentlessly causing a fever to 104 and causing face and neck swelling so severe that she could not swallow her own secretions. It was when she began gasping for breath that her parents rushed her to the Mayo Clinic. And this is what she looked like upon presentation at the hospital. She underwent an immediate I&D because that all -- you know, before antibiotics that's all they had. And that I&D grew staph aureus. She progressed -- she had already progressed upon presentation to develop pneumonia and bacteremia. She described as being moribund by her physician on admission. She was described as having an almost universally fatal infection and her parents were told she would be dead within two to three days. Now Dr. Herrell at the Mayo Clinic was one of the very few people from the United States that had administered what we would consider to be absurdly low doses

 

several orders of magnitude below what would be used in the modern era for a severe infection of penicillin parenterally once per day. Within four days this little girl was afebrile and this is what she looked like at the end of her parenteral therapy before she was discharged from the hospital.

I would submit to you, there are very few drugs, if any, in the entire pharmacopeia that can take a patient who looks like that on day one and turn them into a patient who looks like in a matter of a few days. ICH-E10 reminds us that the determination of margin in a non-inferiority trial is based on both statistical reasoning and clinical judgment. We believe that the data that we've presented are sufficient for non-inferiority margin justification for antibiotics for complicated skin and skin structure infections based on the magnitude of efficacy found, the robustness of the data, the conservative calculations used, our compliance with critical features of ICH and FDA guidance and the critical public health need to make new antibiotics available for physician use for sick patients. And with that I'll stop and open to discussion.

BARTH RELLER: Thank you, Dr. Spellberg. We now have the opportunity for clarifications and questions to any of the speakers in the following presentations from Theravance,

 

Targanta, Arpida and Infectious Diseases Society of America that Dr. Spellberg just presented. Dr. Rex.

JOHN REX: Thank you, Dr. Barth. Actually, I'd like to ask Dr. Spellberg to specifically comment on definitions for cellulitis and erysipelas. I'd like to go back to Dr. Fleming's question earlier and the debate we had for a while about what defines uncomplicated relative to complicated, when is, just to say it loosely, a pattern of cellulitis big enough to count, you know, how do we get at that question of call it the lower end? And I'm specifically thinking about this in the context of developing a drug that might be available only orally as opposed to intravenously. The little girl that you just showed she really needs an IV drug, I can't imagine how you give her something by mouth, but the industry would like to be able to develop oral and intravenous drugs so oral drugs are going to require a patient at the somewhat milder spectrum. And I'd like you to comment from what you've seen about how you would draw that line and with the treatment effect size would be for the kinds of patients you might pick up.

BRAD SPELLBERG: My answer, I think, there are other people in the room that could better answer the question of what the definition of complicated infection is and in fact I would

 

suggest that the committee might want to ask the people who designed these studies and implement the studies. My answer would be I would look at the enrollment criteria in the studies. And the general enrollment criteria for enrolling patients for complicated skin and skin structure infections requires the presence of signs or symptoms of systemic infection. So, you know, it's a substantial skin infection, the presence of a fever or white count is all that you need to be "complicated." There definition than that. But that would be my perspective as someone who reads these studies and someone who takes care of patients. I think that the issue with oral drugs really depends upon oral bioavailability. And if you have somebody -- you're right, I think John, that that little girl would not have been able to take orals because she would not have been able to swallow them. But that if you have somebody who can take orals and you have a drug that 99 percent orally bioavailable I'm not sure I believe there's a big difference between the severity of disease that you'd enroll in an oral versus an IV study. If you have an oral drug with less bioavailability then obviously you would be enrolling patients with less severe infection. I don't know if that answers your question.

BARTH RELLER: Dr. Rex.

 

JOHN REX: Thank you. Almost. Is there such a thing as mild erysipelas? Let me ask it that way. I'm really asking about your large review of the historical data set. You know, it is striking to think about 20 years ago with an 11 percent mortality rate from, I've never seen a 20-year-old die of erysipelas, never did. And yet, if we're going to think about picking up people at the, call it the milder end, when is it enough? And from your reading, can you put any kind of a line on that?

BRAD SPELLBERG: Well, I think that first of all there needs to be a readdressing of inclusion of cellulitis into uncomplicated skin and soft tissue infections because clearly if you have a disease of all comer mortality of 11 percent without therapy that's not a mild infection. So those should -- I think in general, those should be considered complicated and not uncomplicated.

I'd also point out that unlike for an abscess where you can say if you have a mild abscess you can I&D it and it's going to get better 90 to 95 percent of the time you can't I&D a cellulitis. There is no other treatment for it. And so that's also a clear delineation between cellulitis and an abscess. Cellulitis is also complicated because there is no other

 

modality available method to treat it. Where as you can I&D a simple uncomplicated abscess.

If you have a cellulitis in somebody that's afebrile and has no co-morbidities, you might be able to consider that an uncomplicated cellulitis, but I think afebrile cellulitis, a cellulitis in the face of a white count of 15,000, cellulitis in the face of vital sign changes which is a substantial proportion of cellulitis or cellulitis in the presence of co-morbidities, like in diabetes which in the historical literature it was clearly described, diabetes was clearly described as a risk factor for bad outcomes for all of these infections, that those all would be considered complicated infections.

BARTH RELLER: Dr. Rex.

JOHN REX: Thank you. That's all.

BARTH RELLER: Dr. Cross.

ALAN CROSS: I think we have something of a denominator or numerator problem in terms of discussing complicated versus quite surprised on the IDSA analysis, to see that so called minor furuncles were considered uncomplicated. But yet we heard from Dr. Corey that if you look at the numerator of patients with bacteremia and most of those originated from the skin, that presumably, I've always been taught that even with a somewhat

 

mild furuncle that there's always a danger if you lance that of getting a bacteremia. And at that stage it's complicated. So it seems that there really is a transition at some point in time between uncomplicated skin infection then when it becomes complicated and lethal and where that separation is, is a critical thing in terms of the definition of the two types of skin infections.

BARTH RELLER: It would seem that if one is going to consider an evaluation at trials with waiting this concept of, or issue of definitions becomes even more important. Dr. Spellberg, could you reiterate in the literature review how your team categorized major abscesses.

BRAD SPELLBERG: Actually it was pretty easy. Clinicians did it for us in the papers. You know, before antibiotics the dominant school of thought in medicine was the Oslerian school of thought which actually taught physicians in medical school to realize that they could do nothing to change the course of their patient's disease. They actually were taught not to talk about treatment. What they were taught their job was diagnostics and prognostics. That's what they spent all of their time doing. They were probably much better diagnosticians and prognosticians than we are today because they couldn't do anything about any of

 

the infections that they were seeing. And so in all of the literature they actually tell us, "These were major abscesses, these were carbuncles, these were furuncles." And I think when you talk about what's the difference between a furuncle and a carbuncle my naive answer would be, it's kind of like the definition of art, I can't define it, but I know it when I see it. You could probably start to build on that a little bit. If you're febrile with a abscess that's not an uncomplicated abscess that's a sign of a systemic manifestation of your infection, that's a complicated or major abscess. In the Chip Chambers study of the randomized patients Keflex or placebos there were 160 patients enrolled there was one patient who was febrile, 159 were not. Those were uncomplicated abscesses. If the abscess has substantial cellulitis it's a complicated infection. If there's a vital sign formality it's complicated. It there's a high white count it's complicated. We have lots of I think very rational tools that we can use to separate uncomplicated from complicated.

BARTH RELLER: Is there a role of size and is there any correlation between size and systemic manifestation?

BRAD SPELLBERG: You know, there's clearly a role --

BARTH RELLER: -- or physical surrounding -- physical

 

evidence, white count, etc.

BRAD SPELLBERG: Yes. In almost all of these studies they did describe white counts febrility and size and they tended to be quiet large abscesses, often accompanied by high literature. Size clearly should be included as one of the features. Again there are people in the audience who have designed these studies and who could answer that question more precisely than me. So, if you look in the historical literature about what was associated with worse outcomes, size was, location was mentioned, facial, particularly upper lip was very commonly associated with bacteremia and (inaudible) thrombosis, diabetes those were the big and, you know, alcoholism and cirrhosis. Those were the big co-morbidities that were described to be associated with worse outcomes in the historical literature.

BARTH RELLER: Yes, Dr. Gutierrez.

KATHLEEN GUTIERREZ: Hi, I have a question for Dr. Spellberg, too, sorry.

One of the things that I'm struggling with as a clinician and in trying to figure out how to weigh these non-inferiority margins is that I know in many of the patients that we see they all have -- you know, you could conceivably

 

have a patient who had a wound or ulcer infection in with the cellulitis and then developed an abscess. And I'm wondering if you could sort of comment on how you separate all of those in looking at risks.

BRAD SPELLBERG: Yeah that's a really good question. I would say, you know, I would suggest that the way to do that is to do it hieratically. If you have a wound or ulcer infection with a cellulitis that's a wound or ulcer infection, I think that you would sort of work your way down the hierarchically. If you have a wound or ulcer infections with a cellulitis that's a wound or ulcer infection, I think you sort of work your way down the hierarchy.

Because clearly wound or ulcer infections frequently are accompanied by surrounding areas of cellulitis. A more tricky thing is what you do with an abscess which often has surrounding cellulitis around it. It probably depends on the relative amount of affected area that is abscess versus cellulitis. If it's, you know, if it's a two centimeter abscess with half a centimeter rim of cellulitis around it that's an abscess. You know, if it's a 10 centimeter abscess with a one centimeter -- or do it the other way, if its a two centimeter abscess with a ten centimeter area of cellulitis, that's a cellulitis. And I

 

think that, you know, you said "I'm going to take this patient in I&D and give them Keflex even though I know they have MRSA," you probably wouldn't do that with someone who had a substantial amount of cellulitis around the abscess. As a clinician you would know, "I need to treat the cellulitis in addition to draining the pus."

KATHLEEN GUTIERREZ: Right. As a clinician, I think it's an easier question than as in how, you know, do you design a study.

BRAD SPELLBERG: Right. Again, I think there are people in the audience here that perhaps should be queried about when they've designed their complicated skin and soft tissue infection studies, and there are people who have designed a lot

BARTH RELLER: Dr. Septimus.

EDWARD SEPTIMUS: A little different angle. Has anyone reviewed the literature of the modern era with the changing epidemiology in virulence and looked at the data looking at discordant therapy which would be sort of the modern equivalent to a placebo? Is there enough information on there to look at that?

BARTH RELLER: Dr. Rex.

JOHN REX: Ed, let me give you a limited answer. We

 

have done a bit of hunting around for things like that. It's easiest to find them in some of the uncomplicated skin literature. There's a paper, a recent paper, led by a Professor Giordano in which discordant therapy -- well it actually wasn't discordant, it was (inaudible) for a mixture of MRSA and MSSA, you couldn't really tell them apart. But when you read the paper closely the groups are not strongly defined. It's probably like the group that Dr.Spellberg alluded to a minute ago where basically nobody had much of a fever. The details just aren't there. But there was one that we stumbled on actually just very recently it was kind of buried in a paper. Let me read you a sentence out of this. This is from the paper in January 2008, Antimicrobial Agents in Chemotherapy, and this is by Gary Noel of J&J. And it's a double-blind randomized trial with ceftobiprole versus vancomycin. Ceftobiprole, a drug that has gram-positive and Gram-negative activity, that's the important thing, ceftobiprole Gram-positives and Gram-negatives versus vancomycin and it's for skin. Okay? Double-blind, double-dummy so it's a really a nicely done study. It is as modern a design as you can possibly get to. End points, sort of like the earlier conversation, there was a test of cure visit a few days after the end of therapy. But again, double-blind,

 

double-dummy, ceftobiprole with Gram-positive and Gram-negative activity versus vancomycin. Here's the key sentence. It's a big study, so this is a subset that they just commented on in passing. "In the 30 patients that had Gram-negative bacteria identified in the baseline cultures and who received vancomycin alone, 14, 47 percent were assessed as cured at the test of cure visit. This cure rate was considerably lower PA less than .01 than the 81 percent cure rate, 26 out of 32, observed for patients who received keptovipral alone in this analysis of the MITT population." So there's a modern trial design, a very clear discordant therapy involving gram-negatives not gram positive what's the difference 34 percent between the two arms, it lines up perfectly with everything we're been discussing. So that's actually the best one we've found to address that specific question. It's not quite what you might like but it's getting there.

BARTH RELLER: Dr. Nambiar.

SUMATI NAMBIAR: I was just trying to address the question of discordant therapy and I think the study from UCF in minor abscesses a large majority of patients actually had MRSA and they received cephalexin, so that's another example of discordant therapy. And there's another study from Texas in

 

treated with oral beta-lactams and they had MRSA.

BARTH RELLER: Dr. Follmann.

DEAN FOLLMANN: Thanks. I wanted to ask a couple of questions of some of the previous speakers. First I would like to ask some questions of Dr. Hopkins who has slide number eight, I mean slide number nine. This looks at the placebo cure rates for the set of trials and it was used in your setting of a margin for your trial and I'd like to make an observation on that and a technical comment. Just a minute and I'm just trying to bring the slide up. I mean, slide nine. Right.

So this is I guess six different studies, we're looking at the placebo cure rate for these and this was part of what you used to construct a margin in which you compared those with the cure rate in vancomycin. What you've done here is basically assume under this so-called fixed effects model that every one of these studies has a true cure rate which we don't know. But our guess is that it's about .357 and there's some uncertainty around that and in fact I think a more reasonable interpretation of this data is that the cure rate vary from study to study. It's not always the same thing that some studies due to population or the way they are treated or the pathogen in the patient, might have a cure rate which we see there, or a lower

 

cure rate which we see on the other side. And so instead of assuming every placebo trial is kind of the same thing we're always getting the same information, we - I believe there is a lot of variability about the cure rate. And if you did a analysis so-called random effects analysis which allow that there's variability in the true cure rate, you'd get a different overall confidence interval that would be appreciably Wider. And if you look at your margin or your estimate of the margin, M1, based on this analysis it's about 33 percent. If you do a different analysis which allows that the cure rate might vary from study to study, you're margin, M1, the lower estimate of the confidence intervals is about 19 percent so it's substantially less than what you have presented here.

So this is just a comment I would like to make and really it speaks to the question both of the technical methods of combining these studies people are using, sometimes I think it might be more sensible to use something that allows for variability. And it also I think it hits the nail on the head, in terms of my difficulty sort of in knowing how can I assume sort of constancy of these studies. How can I know that what the data I've seen in the past applies to the present. So that was a comment. You know, you're welcome to respond, if you

 

want.

UNIDENTIFIED MALE: I think Dr. Koch will respond.

GARY KOCH: There is a slide that the sponsor has or they may it in the briefing book that actually shows the risk differences for these studies which would have been the comparator versus placebo. And those risk differences are more homogeneous than what you're seeing here in the placebo rates. Can that be brought up? Oh, is that -- which one is that -- that's a different one, that is the random events analysis that differences I think is in a different slides. But let me just continue to speak to that point. The risk differences do tend to be homogeneous.

Now when we go back to the -- well we can work with this slide here. We see heterogeneity in the placebo rates and there's sort of two prospectives for the heterogeneity. One is the heterogeneity reflects random variation of the placebo rates from study to study under the same conditions be which a study would be done and also by the ascertainment of the end point in the same way. Another explanation for the heterogeneity is that these end points were ascertained under different conditions, like under different time points in different settings and that in that context the variation that you're getting from study to

 

study is due to fixed underline causes rather than random variability and what the placebo rate would be. And in that context the estimates that you're seeing within the study variability that goes with the fixed effects analysis becomes more plausible. Certainly if you do a random effect analysis you get a wider interval you get a lower confidence level that's approaching 19 percent and as you did notice, half of that is 10 percent and that still fits with the 10 percent margin. But you're probably doing an analysis with random effects in a setting where the variability between studies is more than just the variability of placebo from one study to another it has some fixed underlying causes in terms of how the endpoint was was ascertained. Just a second, let me bring this slide up.

This is the risk difference and this is speaking to the point that I had mentioned earlier that noted that while these studies had variation in the placebo rate, they were homogenous for risk differences. One interpretation of that would be that the heterogeneity that was seen in the placebo rates, at least in part, is coming because those studies are ascertaining the end point under different conditions as opposed to it simply being a random variation of placebo rates from one study to another.

 

DEAN FOLLMANN: Fair point. I would just say from my prospective, you know, the way that you constructed the margin was to take the placebo cure rates using a method that assumed they're homogeneous when I think there is evidence that they're not and then applied that to the separate vancomycin studies.

GARY KOCH: Again, part of the reason is why that was done was that when we worked with vanco where things were more homogenous, the fixed analysis did indeed again seem plausible although there was some heterogeneity there again. Although again a partial explanation for that could be essentially the in how end points were ascertained.

BARTH RELLER: During this discussion we've had Dr. Follmann answering the questions and the person answering them, please identify yourself when someone is called upon to answer, so that we have a --

GARY KOCH: -- Yes, I'm Gary Koch and I'm a professor of biostatistics at the University of North Carolina and I was indirectly introduced at the beginning of Dr. Hopkin's talk. responded in response to the specific questions. Dr. Follmann, do you have another question?

DEAN FOLLMANN: I just have a few other comments.

So if you applied this kind of reasoning to for example,

 

Dr. Spellberg's analysis that the IDSA does, you also get wider confidence intervals. There are substantial heterogeneity in the cure rates in those studies as they point out in the document. So from my perspective a more rational approach would have been to use a random effects model which allows that there's substantial heterogeneity in cure rates across studies.

The next comment I have is for Dr. Forest. And I'd like to comment on Slide 7 that you presented which showed the relationship between cure and effectively a dose of an antibiotic. And you did some -- implicitly you did an extrapolation, you drew these curves which showed that as you get closer and closer to zero the clinical cure rate drops off substantially. Can you bring that slide up or?

ALAN FORREST: And as you said slide number 7?

DEAN FOLLMANN: Oh, great. Thanks, yeah. So the only point I want to make here is, you know, these curves are drawn without any uncertainty.

I imagine these studies which are there, you know, from the slide there are 134 treated patients, that most of them would have data points where they're at 10, 20, 30 or 5 and that you'd have very few, if any patients who were effectively

 

getting no therapy. So if you draw uncertainties bounds around this you'll find substantial uncertainty about what the effect of the drug is at zero. So while this is kind of nice conceptual study to do. In fact, we don't really have good data to come up with a margin based on this, just because we don't have data in the area that we need it.

ALAN FORREST: In population pharmacodynamics analysis, you're absolutely on target. We definitely compute the standard errors of both of the parameters of the fitted model and if there are regions of interest, we put confidence bounds around that. And of course, the amount of data that is present in a given region is going to affect the confidence bounds. So in a study where there isn't much data anywhere near the lower limit the confidence bounds are unusable because they are large. And likewise, when there's a lot of data pushing past this area you can get tight but also large bounds. And this is a modest size study so you are on target there. But we do this for a living we do a lot of studies. And when you start get hundreds of patients you can get quite excellent precision at that extrapolated intercept.

BARTH RELLER: Dr. Fleming.

THOMAS FLEMING: We've heard a lot of data and the data

certainly establish that antibiotics provide an effect. The challenge that we face is understanding the magnitude of the effect and the settings in which the effect occurs and the impact of setting and the impact of the end point. All of this are comparing to vancomycin and if we are comparing to linezolid and we're similar to the comparator, the question is what does that that tells. Are we similarly modestly effective are we similarly highest effective, are we similarly ineffective? So the data establish an effect but it's very important if you are comparing to an active comparator, to understand the magnitude of the effects in the exact context of which you are doing the study. So factors, there are many factors that can influence outcome. Could I have Slide 14 from the presentation by Charles Davis?

It was the second sponsor -- or the third sponsor presentation. So there are -- if we are comparing to vancomycin the effect of vancomycin can be different across different settings and understanding the effect is influenced by patient characteristics. Slide 14. So in slide 14 suppose linezolid was for example, to be used as an active comparator. Notice here we've been given four different trials and we've been given a cure rate. And we see differences in those cure rates that are

 

quite strikingly different. And in fact if on computes a p value for this cure rate against this cure rate -- in these sample sizes the Z value was about six, p very with many, many zeros, highly significantly different, what is the accounting for this? We have to understand this. Part of what may be accounting for this is that these studies are done in different clinical settings where the kinds of patients that we're treating would inherently have a different cure founding, that's an issue of confounding our predictors. Part of the difference is that the linezolid may have a different effect. It may be in this population of patients having a much greater effect than in this population of patients, that's an effect modifier, or it may be the end point. The definition of the end point can change the overall outcome. The impact of all of this is if you're going to understand the effect of the active comparator, you do need proper control trials that are assessing what that effect is in historical setting. And we've been provided some of that, but unfortunately, as has been repeatedly pointed out, we don't have randomized comparative trials. And as a result we have the potential that factors are both confounders and effect modifiers. So to be specific about this, one of the factors that was very nicely addressed by the IDSA document is the

 

comparison against wound against cellulitis and against abscess. And what we're finding there in the control arm is that the overall success rate is 36 percent, 66 percent and 76 percent. So this is a factor that's clearly a predictor. If you have a difference in the fraction of patients who are wound infection in your historical, untreated population from your penicillin population you're going to get a confounding in your analysis.

Furthermore, these are effect modifiers, the level of effect is greater in wound than in cellulitis than in abscess. And therefore, even if you can estimate the effect of the active comparator it's going to be important that in the non-inferiority trial you have the same distribution of patients you had historically, you have to adjust for the confounding, or guideline has said that if you're going to use historical controls, there are only certain limited settings where they apply. One of the issues is you have to have a treatment effect that's dramatic. It appears that from what we've learned thus far that it is dramatic in cellulitis, it is dramatic in wound infections. Much less clear what the effect is in major abscess. The second issue is the end points have to be objective. And so when these kinds of analyses that Dr. Spellberg pointed out were recently done in CAMP and in fact

 

were just published in the most recent edition of Clinical Infectious Disease both an IDSA presentation and I did Fleming/Powers presentation, the end point was mortality and the effect was dramatic. And so it made sense to use the nonrandomized controlled data to assess the effect of active comparators, penicillin type agents. But ICH-E10 also says the usual course of the disease needs to be highly predictable. Well there's considerable heterogeneity in SSSI and it also the impact of baseline treatment variables on the end point need to be well characterized. So while the IDSA has, to its credit, tried to take into account the impact of extensive disease, both as a predictor and effect modifier, the statement that they're being overly conservative is overlooking the fact that there are many other factors that weren't taken into account. For example, in a CAMP when IDSA looked at age alone, and then Fleming and Powers looked at age and bacteremia, a very different sense of the effect of the of the active comparator changed as you took in account more of these predictors and effect modifiers. So the things that haven't been taken into account here are the differences in the quality of supportive care that exists between the control arm and the penicillin group that's historically been used and the penicillin group

 

historically and what we're seeing today. The effect of antibiotics can change if you have a higher level of supportive care. Age, bacteremia, extensive disease depth and width, presence of furuncles, the IDSA tried to take furuncles out, but in articles where it wasn't clear which patients with furuncles and which weren't, they are left in to my knowledge. And that was true in almost 50 percent of the patients that were there in their active control group, but only 10 percent of the penicillin group. So there appears to be a substantial risk that there are imbalances in very predictive factors and in effect modifier, i.e. factors that can influence how the treatment is working. And these are the issues that greatly lead to the need for caution in interpreting what is the actual effect of in this case if we're using vancomycin or linezolid, what is the actually effect if your trying to show that your therapy is not meaningfully worse.

Let me ask just a couple of quick question that are related to this for the IDSA presentation. The first of these is the IDSA presentation, in fact, in their article says on page 16 that microbial agents continually lose efficacy over time. And one of the issues that is an effect modifier is a level of resistance. We are estimating the effect of these active

 

1950 prior to resistance. Now we are applying this to today's active comparators such as vancomycin for which resistance is developing. And by the IDSA's own indication, these are agents that are continuously losing efficacy over time. How does that not undermine the interpretability of your estimate of the the active comparator? We're taking penicillin's effect when there was no resistance, no resistance and applying it the effect of today's active comparators, which by IDSA's own indication are Active comparators that are treating population where there is emerging resistance. So how does -- that's question one, how does that reality not undermine your estimate of the effect of the active comparator?

BARTH RELLER: Let's take Dr. Fleming's one at a time, questions. Well, Dr. Spellberg.

BRAD SPELLBERG: Well I would like to make a couple of comments. First I want to thank Tom for pointing out the strength of our analysis, not the weakness of our analysis. You cannot enroll patients in the clinical trials, and we make this point in our manuscript, if the patient who's being enrolled is resistant, has an organism that's resistant to the comparative drug. That's why it is relevant, specifically, to look at the historical data during the period at which the

 

comparator drug was active against the majority of strains circulating. Because if you have an organism that's resistant to the comparative drug you are excluded from enrollment in a modern trial. So that's exactly why we did choose to look at era of coverage.

THOMAS FLEMING. So one of your points here is to ensure that there is no, in essence, a diluting away of the fact. It's imperative to verify that any patient entered into a modern day trial does not have resistance to the active comparative agent?

BRAD SPELLBERG: Oh sure, but that's already done, that's standard.

THOMAS FLEMING: But that's an important point to keep in mind as we move forward to --

BRAD SPELLBERG: Tom, can I make a couple of other points? One, the furuncle issue. You're correct for the sake of time, I didn't have time to go into how we handled that. In the primary analysis there were some studies that blended together carbuncles and furuncles and we simply couldn't tell who had a furuncle or a carbuncle.

THOMAS FLEMING: That's right.

BRAD SPELLBERG: That constituted less than 10 percent of the patients in the primary analysis.

 

THOMAS FLEMING: Well on my account it was less than 10 percent of the patients in your active arm, in the penicillin arm, but it was 47 percent of the patients in the control arm, by my count.

BRAD SPELLBERG: That's not -- I do not believe that's correct.

THOMAS FLEMING: Okay, so that's something to --

BRAD SPELLBERG: But the second point to make though, is -- to address that, we did a sensitivity analysis looking just even mention the word furuncles and there was no difference in cure rate in that sensitivity analysis.

THOMAS FLEMING: The analysis -- a strength of the analysis is taking into account wound infection against cellulitis against abscess. But many of these other factors have not been taken into account which could similarly -- and what your analysis shows is that that factor is very much both a predictor and effect modifier, i.e. patients overall outcome left untreated varies significantly across those factors and treatment effect varies differently across those factors. Yet none of an array of other factors were taken into account in your analysis. Now, obviously, in a sense your trying to address that with the consistency assumption -- addressing the

 

consistency assumption, but in particular to the extent that you can't, your trying to account for that by using the confidence interval approach and preserving the half the effect. But your comment is this is being overly conservative when in fact if there are confounding by many of these other factors that you have to take into account, it may not be conservative at all.

BRAD SPELLBERG: Well, we tried to be as conservative as was feasible based upon the data that we had available to us. And I would also point out that when you look at the mortality rates for these infections it would be unbelievably --

THOMAS FLEMING: We're not talking mortality --

BRAD SPELLBERG: -- no, but the point --

THOMAS FLEMING: -- I'm sticking with --

BRAD SPELLBERG: -- no, but the point is is if you're saying that there are differences across patients and standard of care and all of these things, when you look at the year by year mortality rates and see an instant immediate massive decline in death, the year that antibiotics become available and then that mortality rate stays the same over years --

THOMAS FLEMING: So you're getting back to an issue that we've already conceded. These interventions have an effect in this setting. A sense of the challenge is getting an

 

understanding of the magnitude of the effect particularly on the end points that you're using and then the settings in which the effect occurs. So the subtlety here, the issue that's more difficult will be getting into understanding the effect, for example in major abscess. Or getting -- understanding the effect in uncomplicated. But let me just raise one more question at this point and we can discuss issues later on, the idea --

BARTH RELLER: Excuse me, after lunch we'll be able to continue this, but let's finish with this --

BRAD SPELLBERG: I won't be here after lunch. So if there's anything you want to ask about IDSA --

BARTH RELLER: We will shift out lunch slightly because I think it's very important to try to address these things while we have the opportunity with Dr. Spellberg being with us. Thank you for clarifying that. Dr. Fleming.

THOMAS FLEMING: So one other question at this time. I think one of the strengths of the IDSA document is an attempt to implementing. And it's the end point on your Slide 3 that basically has about eight components that are -- rather they are working towards achieving something that is more objective which is very important from ICH's perspective. One of the

 

interesting and it seems to me fairly intuitive comments that was made in the IDSA document on pages seven and eight is that not all trials in fact allowed us to assess. This isn't the page, but it's Slide 3 where they list the different components that define failure in their clinical cure definition. Keep going ahead, there it is. And what they note is that the cure rate increases when factors used in the definition of failure decrease. So what you had obviously understandably recognized as acrossed all of these trials, not all of these components were assessed. And as you assess fewer of these components defined for failure, obviously the cure rate will go up. And it does point out one other critical issue and that is the margin that we use will be very specific to the end point and the magnitude of effects that we are looking at will be specific to the end point. If you have an end point that is defining cure rate based on much less than this amount of information then the cure rates could be upward toward 80, 90 percent. Whereas, if you have cure rates when you're looking at more of these components it could be 70 or 80 percent. The margins that we would use therefore, are specific to the exact definition of the end point. So it's another insight that comes from here. The bottom line here isn't what it is the margin. The bottom line

 

is yes, there are settings in which there's clear benefit. What are those specific settings? What are the specific types of patients? What's the nature of supportive care in those settings and what's the specific definition of the end point? Because all of those can influence what the actual margin should be.

BRAD SPELLBERG: Yeah. I totally agree, Tom. I mean you're absolutely right. And in fact one of the and I appreciate the opportunity to comment on this because this gets brought back to something Dr. Follmann mentioned before about heterogeneity.

One of the features that was actually quite striking, and in the manuscript we have a comment section and for each of the articles that we've referenced where we described what in that study defined failure, what they describe as their outcomes that we could include as failure. And what you find is that over time, not surprisingly perhaps, more and more things -- as the science of clinical investigation was developing over that half century period more and more things were being included in the definition of failure over time. Older articles tended to describe fewer things that you could use to describe as failure. So what that did introduce heterogeneity, but it introduced

 

heterogeneity in a manner that biased away from antibiotic efficacy because the older studies without antibiotics were describing fewer factors that you could use to define failure and therefore were artificially inflating their cure rate compared to the newer studies.

THOMAS FLEMING: So in the essence, when we've had some presentations given to us saying the cure rate in the control arm in untreated patients is around 50 percent, those are meaningless statements because there's a wealth of data to indicate that the cure rate is going to be very substantially different based on the characteristics of the patients -- untreated, even untreated characteristics of the patients and the definition of the end point. The end point has a great influence on the actual success rate that you would have.

BRAD SPELLBERG: Well, I question the -- here's the way that we looked at it. Yeah, which I think may be reasonable. If the cure rate that's being described in the control arm is artificially high because they're not getting a lot of factors that could lead to failure, it provides an accurate floor for the minimal effect size of antibiotics. And so I don't think it's meaningless. I agree it's imprecise, but what we've said is that we believe it's imprecise in a manner that is contrary

 

to inflating antibiotic efficacy. If anything it deflates the apparent antibiotic efficacy.

THOMAS FLEMMING: It may or may not. There are two assumptions you're making.

First, is that you are systematically having fewer factors in your definition of failure in the historical setting. The other assumption that you're making is that the nature of treatment effect is the same across different definitions of the end point. And that's patently wrong as well. Treatment effects differ according to the nature of your defined end point. So the right answer here is to have properly controlled trials that tell you the historical effect of the active comparator and then to understand which of those factors are effect modifiers and then take all of that into account when you're analyzing the non-inferiority trial.

BRAD SPELLBERG: We totally agree, Tom. That would be the ideal scenario, and unfortunately we don't have it. We have to make the best with what we have, I think.

BARTH RELLER: Thank you Dr. Spellberg. We have three hands up. We'll take those three and then we'll have lunch. Mr. Levin.

 

ARTHUR LEVIN: Thank you. On page 50 -- this is for Dr. Spellberg. On page 50 in your bar graph, which shows the drying up of a pipeline for antibiotics. So I'm not sure what the point is here. Is the point that a relaxation in the standards -- in the approval standards is what we need in order to reverse that pipeline?

BRAD SPELLBERG: We're not talking about --

ARTHUR LEVIN: If you put a straight edge on those bars its a constant trend over time so is there evidence that something about approval standards has led to the drying of the pipeline? And that if those approval standards were changed that pipeline would suddenly flow with new antibiotics?

BRAD SPELLBERG: No, no, no. I'm sorry. I'm sorry if I gave that impression. The issue here is not relaxing approval standards it's clarifying approval standards. The approval about relaxing them to beyond what the standards used to be. It used to be quiet common to use a 15 percent margin, for example. The issue is if a company doesn't know what the regulatory standard is it's not going to take the risk of investing R&D into a drug that it could do all these studies for and at the end when it comes up for review they say, "Well the standards have changed, we're not going to approve your drug." We're not

 

seeking relaxation, we're seeking clarification. We want a clear standard. Tell us what the studies need to be. And that's what you guys are here to do. We're not saying we want 10 percent better than they used to be. No, no, no just tell us what they are. Clarify what they are so companies know what they need to shoot for when they're developing a drug. Does that make sense? I hope so.

BARTH RELLER: Thank you, Dr. Spellberg for emphasizing what our sizeable task is this afternoon. Dr. Goetz and then Dr. Rex and then lunch.

MATTHEW GOETZ: This is probably also for Dr. Spellberg. But just a comment on the effects size versus microbial resistance. I fully and we all fully acknowledge the patients who have defined resistance of their pathogen won't be enrolled in studies. But recognizing there -- it's a gradient effect and one of the concerns that of course infectious disease communities are concerned about is the relative loss of effect of vancomycin, even for strains of staph aureus that are within the defined susceptibility range. And thus, do you have concerns that your treatment effect might be magnified? When we're looking at penicillin in an era where we were using, as you showed 20 to 50,000 units of penicillin highly effectively,

 

and now our standard comparator is vancomycin when we're dealing with hetero-resistant strain of MICs of one, MICs of two and the decreased effectiveness of vancomycin.

BRAD SPELLBERG: Oh, it's an outstanding point, Dr. Goetz. I mean there's no doubt about it. I mean, it's not just an issue of what the lab says, S or R. And I think you've pointed out the one drug that that's most concern for, vanco.

Again, what we tried to do was, to the extent possible, and Tom forgive me, to the extent possible with the data available we tried to be conservative. Because clearly this is something you guys need to factor into when you set what the margins should be. Maybe that means that vanco should no longer be the drug that's used because we haven't seen an MIC creep for linezolid for example. I don't know, but that's one of the factors that should be discussed. You know, the bottom line is it seems like you've heard four or five different strategies. All of them imperfect. Every single thing we've done is imperfect because as Tom has totally corrected pointed out the only way to do this perfectly is to have a double blinded randomized placebo trial and we don't have them. So we've all tried to do our best in an imperfect world. And you've heard four or five different strategies to address this issue. All of

 

which are done by different groups using different approaches and different methods all lead you to a very similar estimate of improbable to end up with the same exact numbers using a bunch of different methods. So all I can say is, okay, that's fine, but all I can say is that we did our best within the constraints of the data available. And now you guys have to make a decision.

BARTH RELLER: Dr. Rex.

JOHN REX: Two things. Dr. Levin on behalf of industry what I would say is that we are desperate for stable rules. It is important to understand how many years elapse between identifying a molecule in the laboratory and arriving at a conversation like the ones we are going to have the next two days and the submission of a data package. It's not days, it's not weeks, it's not months, it's not even a couple of years, it's many years. It may be 10 or 15 years. You've got to know where you're going when you start. Otherwise, businesses will not invest the prodigious sums required. That's my comment right there.

Specifically to Dr. Fleming, who asked us some comments about end points. You're correct. That is we must be clear about the end points. But the idea that you can -- that we

 

cannot make use of the older data, I do have to conception with you there, because let me say this again carefully. In a modern trial the collection of symptoms that gets us to the end of the observation period with a check box that says is the patient better or not? Think about that final checkbox, you know, every casebook has a place where you say succeeded or not and you check. What got you there is not a single thing. It's actually an extended conversation between the patient and the physician. And along the way, on day one, on day two, on day three, the patient has lots and lots of opportunities to bail out and fail. "Doc, I feel bad. Doc, the drug is making me throw up. Doc, I still have a fever." There are lots of ways to get out. And all the data that we've looked at points at the fact that you're going to punching eject on people earlier because they fail. But you never punch eject early because they succeeded because you can't do that. The only way to get to the end is by being clean the entire way. So, I think we are going to have to deal with an integrated sum of clinical response. And even though it may well be that the older data are prettiest, at least the report that we have is prettiest to day two for that particular piece of the extended conversation between the patient and the physician.

 

Everybody who has been to medical school and who has taken care of these people knows that there is a mapping from that day to the final event. It's not that hard to see clinically. And so that's I think the thing that I want us play with. The data we have are not satisfactory. We do not have everything we want. But I think we've got enough that if we will combine the statistical criticisms with our medical knowledge, we actually can get at a reasonable spot. So that's my plea for this afternoon and my comment to Drs. Fleming and Levin.

BARTH RELLER: From the spirited discussion this afternoon.

Instructions for the committee, in the Prince George's Ballroom, there's a separate room set up for committee members just across the hall. And again, there will be ample time to hear everyone this afternoon. Please no discussion of these matters during our lunch break. We will reconvene at 1:15 p.m. Thank you.

[Lunch Break]

BARTH RELLER: -- To our Advisory Committee on meeting deliberations. we'll open this afternoon with the open public hearing. We have one speaker, but before hearing from our

 

speaker, I should like to read the following statement:

"Both the Food and Drug Administration and and public believe in a transparent process for information gathering AND decision making. To ensure such transparency at the open public hearing session of the advisory committee, FDA believes it is important to understand the context of the individuals' presentation. For this reason, FDA encourages you, the public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationships that you may have with the sponsor, sponsors, their products or if known, its direct competitors. For example, this financial information may include the sponsors payment of your travel, lodging or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

 

That said in many instances and for many topics there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy and respect. Therefore, please speak only when recognized by the Chair. Thank you for your cooperation. Dr. Newman (sic)

Let me get the first slide up.

SUSAN NICHOLSON: Good afternoon everyone. I'm Susan Nicholson. I'm an employee of Ortho McNeil Jansen Scientific Affairs which is a division of Johnson & Johnson. And my relationship to the other sponsors depending on how things will go over the next couple of days, we will be competitors. My comments today will focus on complicated skin and skin structure infections.

We're grateful to the FDA and IDSA for their efforts in compiling the data and providing sound rationale for the non-inferiority study designed for complicated skin infections. The FDA and IDSA consider complicated skin infections as inclusive of several infection subgroups namely cellulitis,

It's worth noting that diabetic food infections were excluded from the list. It was proposed that the skin infection

 

types or subgroups be separately considered in terms of placebo cure rate determinations. While we agree that the skin infection subgroups may be considered separately for the purposes of sample size determination, these subgroups represent a continuum of complicated skin infections type. And that's we agree with the recommendation to combine the spectrum of subgroups in order to compile the study groups. We agree that for our Phase 3 studies in complicated skin infections that a non-inferiority margin of 10 percent is adequate.

The FDA and IDSA discuss skin infections as a collection of subgroups. The skin infection subgroups represent a continuum of disease. A patient with a complicated skin infection predominantly characterized as an abscess may have substantial surrounding cellulitis which requires antibiotic treatment even after the abscess is drained. Similarly, a patient with cellulitis may have an associated deep tissue abscess. In these mixed infection cases is that a patient an abscess or cellulitis patient or simply a patient with a complicated skin infection? The basis for effective therapy is the same for all skin infection subgroups. The potential pathogens are similar and all require an appropriate amount of drug to reach the site of infection, i.e. the skin interstitial

 

fluid. Like the FDA, clinicians also consider the subgroups as part of the same disease. We cannot think of an example where an antibiotic was effective in treating cellulitis due to a particular pathogen, but not effective in treating an abscess or a wound infection due to that same pathogen. Differences may occur in skin type cure rates due to variable antibiotic activity. It is therefore important to include wound infections, cellulitis and abscesses in a clinical study to comprehensively capture the experience with a variety of causative the pathogens.

I think I'm ahead of myself. Let's go back. A complicated skin study should include patients from all subgroups so that the study can cover different infection types, infections with different severities and infections due to a variety of pathogens. A reasonable approach is to separate the subgroups as has been done by both the FDA and IDSA for the purposes of placebo cure rate determination. The study of skin infections should address the combined subgroups as discussed on the previous slide.

Skin infections comprise a continuum of disease with the same pathophysiologic principles apply. In order to balance the treatment arms, the study arms could be stratified for the

different infection types to reflect the different cure rates for the subgroups. Clear definition of infection types is required.

An expectation in a study of these combined infection types is that there is consistency and clinical and microbiologic response across the spectrum of disease. The approach of an in depth analysis of the antibiotic treatment or placebo cure rate has a clear value when calculating the non-inferiority margins for skin studies. We considered the possible evolution of this line of thought into considering each of these subgroups as distinct entities and the implications that would have to development of new antibiotics for skin and soft tissue infections. If the subgroups were studied separately would efficacy in a single subgroup or two of the four groups imply efficacy in the other subgroups? And how does diabetic foot infection fit into this paradigm? The only mention in the background material of diabetic foot infections or diabetic foot ulcers associated infections is in the question the FDA imposes to the advisory committee. DFI may be construed as a separate consideration, but this issue cannot be vetted in depth at this meet without providing some background information to the committee. Importantly, DFI is a complicated skin and soft

 

tissue infection to clinicians not including DFI in the cSSSI guidance will in effect exclude these patients from pivotal trials for new drugs, thus denying clinicians critical data to assess a common clinical scenario.

In conclusion, the spontaneous, excuse me, subgroup consideration is very valuable for justifying a placebo or spontaneous cure rates for cSSSI. Non-inferiority study design is appropriate in skin infections studies since mortality associated with failure across the spectrum of disease as has been discussed. And importantly, guidance on DFI, diabetic foot infection, is a key subgroup of complicated skin and soft tissue infection and is absolutely needed. Thank you for your attention.

BARTH RELLER: Thank you Dr. Nicholson for correction in the record. Dr. Nicholson whose just spoken at the open public hearing. The open public hearing portion of the meeting is now concluded and we will no longer take comments from the audience only the voting and nonvoting members of the committee. The committee will now turn its attention to address the task at hand the careful consideration of the data before the committee as well as those public comments.

I'd like to next outline the process that we'll follow

in considering the discussion in the question session. After the discussion is complete on each of the questions posed we will vote. The voting is electronic. It's a new voting system. Each of you has three buttons on your phone. This is the lower rank of buttons. And each of you is to vote yes, no, or abstain. Once we begin the vote, press the button that corresponds to your assessment. We'll have about 20 seconds. It's like the clinical questions at the IDSA. After everyone's completed the vote, the vote will be locked in, tallied and displayed on the screen. I will read the vote from the screen into the record.

Next, we will go around the room and each 22 individual who voted will state their name and vote into the record verbally, as well as the reason, the essential reasons, why they voted as they did. Consequently, it's very important that we have a full discussion before the vote takes place because we do not want to reopen a discussion. One can explain your vote, but question each other, clarification of data and the like. All clear?

Okay. So our first question is, are non-inferiority trials acceptable for the indication of complicated skin and soft tissue infection? Discussion?

Among the participants that I know wanted to comment

 

during this portion of the meeting is Jeanine Thomas whose a patient representative from the Methicillin Resistance Staph Aureus Survivors Network. You don't need to speak now, but this would be the time frame into which to introduce your comments and valuable prospective. But it's open now the discussion for all committee members voting and not voting on this particular topic. Yes.

EMIL PAGANINI: One of the reasons why I'm here, a nephrologist, is complications of any new drug and it's comparison with whatever standard. In the presentations this morning and in any of the questions that were asked no one addressed any of the complications of the particular drugs comparing them whatever the comparator was.

It seems that there is some specific renal complications that were addressed both in animal studies and in the pre-work that was given to us and also in some of the clinical outcomes. And I'm wondering that if we are to use non-inferiority as our method and we only look at principle outcomes are we not also -- should we not also look at other issues such as complications of drugs in other areas. For example, acute kidney injury if caused by a drug carries with it a morbidity and mortality in and of itself so an enhanced incidence of acute kidney injury by

 

using a drug may make that comparative statement much different then if we just purely looked at the mortality or effectiveness. So I was wondering if the committee wanted to address that issue.

BARTH RELLER: Thank you, Dr. Paganini. Responses from other committee members, statistical expertise teasing out this effect? Dr. Rex.

JOHN REX: A good point. And the entire morning has been about the efficacy side of the risk benefit equation. The whole area of formal approach as to risk benefit is a very important one. And, you know, I think we really should define the two conversations because if you don't -- if you can't establish that you believe there is an effective therapeutic effect on the disease under study than the issue of adverse events downside of a drug becomes irrelevant. But we need to get over the question of efficacy which is what we've been debating. And then a medical risk benefit decision has to be made and industry is used to doing that. FDA definitely does that. There's a whole discipline that is currently developing this. And so I am sure we will -- you will have that discussion over the next couple of days. But the decision now is a focus on how do you get out of the benefit side of what we're trying to measure. But that

 

would be my general answer to your question, but you've raised a very important integrative point about risk benefit overall. You do have to come -- that's the last step in the whole

BARTH RELLER: Dr. Cox.

JOHN COX: Thanks, Dr. Rex for your comments. Today a lot of the focus is on what we can understand about treatment effect and clinical trial role design. That's not to say the safety issues are of equal importance. And as we work through the issue of trying to understand treatment effect and trial design as Dr. Rex has said we'll come back to the issues of risk and benefit as we get to specific drugs and dealing with the safety profile of the drugs and what we know about the benefit of the drugs.

I thought, Dr. Reller, it might be helpful too to come back -- there was some discussion over the course of the morning about uncomplicated and complicated skin and skin structure infections. And I might just make a comment on that since that's the question that we're dealing with here first and that's the issue of complicated skin and skin structure infections, just to provide what I hope will be some clarification on complicated skin and skin structure infections and how that we've looked at them from a regulatory standpoint. So complicated skin

 

infections tend to be those that are deeper, soft tissue infections are those that require surgical intervention. And that's differentiated from uncomplicated skin infections which tend to be more sort of cellulitis, impetigo and within that group is furuncles. So it's not strictly a definition just solely on severity, but it's also the characteristic of the particular condition. Now it also also happens that, you know, despite this sort of major driver being deep soft tissue and the need for surgical intervention versus those infections where you don't need -- or you either don't have deep soft tissue involvement or the need for surgical intervention. Severity does sort of naturally correlate with those two sort of anatomical differences you will in the types of infections. So I just provided that what I hope is some agree of clarification. There is heterogeneity here, you know, there is overlap to some extent, but I hope that provides a little bit more information on sort of the genesis of how we got to complicated and uncomplicated skin infections.

BARTH RELLER: So a part of that would be the probability or likelihood of ancillary therapy in addition to the antimicrobial. And it relates back to the discussion of the different groups and the possible numbers associated with the

 

non-inferiority margins and implicit in those when you see the different numbers, for example, in Dr. Spellberg's presentation, it's sort of implicit in there that a lesser role of antibiotics where's there a greater role of ancillary therapy. If I understand Dr. Paganini's query and clearly in each of the sponsor's presentation ultimately there will be, in the overall assessment the risk versus benefit. But I think there was a component of that and that's why I asked for some statistical help, is not what the overall risk benefit is, but how that component might affect the attributable role of the antimicrobial itself in assessment of effectiveness. Dr. Fleming?

THOMAS FLEMING: Well, this is a key point that Dr. Paganini's raised and that you're pursuing Dr. Reller, I'm not sure I'm going to answer the attributable role part. But it is absolutely on target to talk about the issues of risk and off target effects as one thinks about benefit to risk and as one thinks about the bar or the threshold for how much benefit you need in order to have favorable benefit to risks.

Historically, when we have talked about non-inferiority trials as we have done for decades and in developing the science, we recognize that we are allowing the experimental

 

agent to be worse. And the issue what is that threshold for what's an acceptable level of being worse. And in many settings we have tried to motivate this based on a new therapy that in some sense is better on other measures, is better in convenience, in safety, cost and etcetera. Generally from a regulatory prospective we would look at better in safety and better in convenience. So if you have a agent that has an 80 percent success rate and let's go with the IDSA, definitions, you have been a 20 percent failure rate. So you have 20 percent of people that either have septic complications that have progressive worsening of infection, failure to heal wounds, failure for skin graphs, amputation and et cetera. You got a 20 percent failure rate.

How much for are you going to allow before it matters to patients? And even if you say you want a margin as big as 10 percent; you're saying it's acceptable to have a relative 50 percent increase in that failure rate before it's unacceptable. Now generally that's really pushing the limit as to what would be clinically relevant. And by the way, M2, what's been missing in the discussion this morning is M1 is your estimate of the effect and that's incredibly noisy and with potential risk of bias because of the effect modifiers and cofounders that haven't

 

been accounted for. But essentially when we come up with that estimate M2 is basically saying you want to preserve half the effect. But the other part of M2 is -- and that margin also has to be small enough that a patient and/or caregiver would say it's acceptable to have that much loss in the context of what you're gaining. And here's where that safety issue is very important. If you anticipate that your antibiotic will be better in terms of cardiac toxicity, renal toxicity, liver toxicity or some other domain that could be a better basis for justifying that I could allow up to a relative 50 percent increase in failure, a 30 percent rather than 20 percent failure rate. So this is something to keep in mind. And certainly if on the other hand your antibiotic is worse in the safety profile then it becomes extremely difficult to justify that it's okay to also be up to 10 percent worse in efficacy. So these are issues that have to be carefully thought through as you justify the margin.

Again I keep coming back, if we walk out of here today with the thought that there's an answer, the answer is a 10 percent margin, without thinking about the context of relative safety profile or relative patient population or nature at the end point, we're greatly oversimplifying the challenge that we

 

influence the justifiability of a margin.

BARTH RELLER: Dr. Alston.

KEMPER ALSTON: From the clinical standpoint, I think safety is very important for this meeting because of the nature of the infections that we're treating and that we do have a lot of approved alternatives. You know, the controversy would be HIV disease which is uniformly fatal and even worse situation with the resistance where we tolerate tremendous toxicities because we have no alternative. You know, for these infections, we can still give vancomycin, we can still give linezolid and we're quibbling over a few percentage points here and there. So, I think in the context of this meeting, I would just argue as a clinician that we need to take the safety issues more seriously than perhaps for some other infectious diseases.

BARTH RELLER: Dr. Nelson.

LEWIS NELSON: Thank you. And I appreciate you bringing up that as well. You know, I'm here as, I guess, as a medical toxicologist as somebody who thinks about adverse effects of a drug as my career. I'm also an emergency physician and as I think about managing many of these cases we're talking about today, and this does come back to safety to some extent, is that I always treat patients based on empiric diagnosis. And when

 

you take a drug from the setting of a clinical trial and you bring it in an emergency department or into a medical ward where you're just treating people based on a presumed diagnosis not necessarily on the base of an expert opinion or basis on a microbiological diagnosis, I think that really changes the nature of the safety of the drug as well as the efficacy of the drug. And I guess what I'm having some trouble getting my hands around is how you apply that to a situation like this. And I don't know if there's a statistical answer or if it's just one of those clinical answers doctors have to do the best job they can, but somehow when we look at these risk and benefits of drugs, I think we have to realize that the situation that we're going to be using them in is quite different than the situation that they're used in clinical trials.

BARTH RELLER: Thank you. Ms. Thomas.

JEANINE THOMAS: There's factors that could affect the outcome and were not addressed in patient's safety from the sponsors. And I would at this point like to give those questions to them. Would patients who had MRSA infections, did they have prior infections and if so how many infections?

Were patients with MRSA screened for MRSA prior to or after treatment for colonization? If so, was rapid testing used

 

or clinical microbiology cultures? Was there any sub typing done to determine the strain of MRSA so that you could track what your antibiotic was working better with on different strains? I'm very concerned also about the irritability in regards to vancomycin. I was on vancomycin for a very long time, I know how painful it is, the swelling. And I see that some of the antibiotics were shelved again because of that originally. So I'm very concerned about the painful administration of the antibiotics. And, as we know, if you're colonized with MRSA you is very, very important within a study.

BARTH RELLER: We may have to repeat those queries, but anyone from the sponsors who were in the context of assessing the utility of and the margins appropriate for a non-inferiority trial like to address any of these questions related to the trials undertaken?

Screening for MRSA, anything that relates to the study design of the trials that would relate to the questions Ms Thomas asked. Dr. Corey.

RALPH COREY: Can we go through those questions one at a time again, please.

JEANINE THOMAS: For patients who had MRSA in your studies, did they have prior infections before entering the

 

study?

RALPH COREY: Often they did. The study that we did -- the two studies we did that were identical tried to enhance for infections with MRSA and that included enrolling patients who had previous MRSA infections, yes.

JEANINE THOMAS: So there was a thorough history given to the patients of how many infections, what they were treated with what antibiotics they were given for their infection?

RALPH COREY: As thorough as we could. I think a lot of these patients had multiple infections. But what we were trying to figure out who was at highest risk for the present infection -- for MRSA in the present infection.

JEANINE THOMAS: Were any of the patients screened for colonization?

RALPH COREY: Before the trial, no.

JEANINE THOMAS: Or afterward, after their --

RALPH COREY: I think that depended on the sites a lot of these sites were in the U.S. and yes they were and a lot of the sites were outside of the U.S. and I would aspect that they weren't, but this was done on a medical by the physician treating them and not as a part of protocol.

JEANINE THOMAS: Was there any sub typing done --

 

RALPH COREY: Yes.

JEANINE THOMAS: -- to find out what the strain was?

RALPH COREY: We know Vance Fowler took all of the isolettes with MRSA in the study and has looked at them extensively for much more than strains, but also for virulence factors, for toxins, everything you could think of or at least everything that I could think of.

JEANINE THOMAS: So are you looking for U.S.A. 300, U.S.A. 400 different strains?

RALPH COREY: Yes, that was the easy part. The hard part was looking at the different virulence factors and seeing if there was outliers in different countries and different sites and different infection types.

JEANINE THOMAS: Okay. Also about the skin redness and the irritability from the veins because of the antibiotics were there consideration of modifying?

RALPH COREY: Well, this was captured as a safety on the CRF as part of the adverse effects and that's one of the issues But I don't think we went further then just capturing and leaving it to the physician on site to decide whether it needed to be changed, the antibiotic needed to be discontinued or that catheters needed to be changed out.

 

JEANINE THOMAS: Do you know if it was regular catheters or pick-line?

RALPH COREY: I do not. I'm sure they were very variable, depending on the site. And how long you decided to treat the patient.

JEANINE THOMAS: Okay. Thank you.

BARTH RELLER: Dr. Gutierrez.

KATHLEEN GUTIERREZ: Hi. I just wanted to bring up the issue of the comparator drug which I'm trying to understand. I know that a lot of information that was presented this morning used penicillin for the beta-lactam antibiotic as, you know, our gold standard. And, you know, the comparator drug that's being used in recent studies is often vancomycin. And I guess my question is, for Dr. Nambiar, were you able to go back and find out any information about vancomycin's efficacy relative to a beta-lactam antibiotic in the non-MRSA era? Because you know as infectious disease doctors you know, we always are taught that beta-lactam antibiotics, you know, have more rapid killing, they have better penetration into different areas and I'm just wondering how you feel vancomycin compares to a beta-lactam for Methacylin susceptible staph aureus infection?

SUMATI NAMBIAR: I don't think we did any specific

 

analysis looking at that, but some of the older studies where the comparator agents were vancomycin to start if MSSA was identified an option was provided to switch to semi-synthetic penicillin. But we didn't go back and do any other analysis.

KATHLEEN GUTIZERREZ: Thank you.

BARTH RELLER: Dr. Follmann.

DEAN FOLLMANN: So the question that I have or the main issue I have really having to do with bridging the imperfect studies that we have TO setting up a margin. And I'll accept, you know, that antibiotics work. The problem for me is how do we come up with a specific margin for the current antibiotics we have because they have to be -- the margin has to be specific to the trial in which the study is being conducted. So that means the host population, the pathogen population, the levels of supportive care, maybe they're getting something for gram-negative organisms or anaerobic organism. And so because it -- and also it depends on what kind of infections we're looking at. And so we have to get specific if we want to come up with a specific number for a margin. And based on all the studies that I've seen so far today and that I've read, two that I think are -- that provide the best evidence for me are the FDA's impetigo studies which show about a lower confidence bound

 

of about 18 percent. And the question there for me is how do you bridge impetigo to the kinds of complicated SSI infections we're considering here? So that's one issue I guess, impetigo could bridge reasonably well to cellulitis, I don't know about the other infections. So that's one question. And the other line up with the kind of studies we have to consider in modern era was Theravancin's analysis and I wanted to have more commentary on the kinds of population etcetera they had in the vancomycin trials that they looked at there. There lower bound was about 20 percent doing a random effects analysis for that. So I guess the question is for Theravancin to give a little more detail about the populations and so on of the vancomycin trials they used.

Another question I'm sort of struggling with is major abscesses which is one of the major categories we have. I want to better understand if they're are minor how well they're treated with incision and drainage and could a placebo effect -- could there basically be no difference between a placebo with drainage incision incision versus drainage incision. So to me, you know, the abscesses are also a difficult wound category to deal with because I think maybe they could be treated with non-antibiotics fairly successfully.

 

BARTH RELLER: Dr. Corey will respond to Dr. Follmann's questions.

RALPH COREY: I'm not sure I got the first question. The second question about abscesses is a difficult one.

I think it's -- it's like Dr. Cox talked about with uncomplicated versus complicated skin infections. They get blurred and I think if we all had big abscesses we need large surgical drainage that with a lot of tissue destruction, all of us would concede that those do need antibiotics. However, the smaller the abscess probably the less likely they do need antibiotics as in Chip Chamber's trial, which is an interesting trial to look at. Because if you look at that trial what he found was two arms, keflex which was an ineffective and placebo which is ineffective. And the cure rates were 84 and 90 percent. If you look at those two numbers and say okay they're all placebos let's put them all together, our cure rate's is 87 percent and then you look at Rue's data from Arkansas that said okay, I'll look back at the placebo cure rate and in a group of abscesses and it was exactly 87 percent, but then he had a group of case control that said, well those were the ones that were treated and their cure rate was 95 percent. He said, "Okay, well that's eight percent difference in the two that's probably

 

a pretty nice estimate of rather middle sized abscesses," okay. Smaller abscess, I would agree, we don't need antibiotics for and I think that's one of the things that I would like from the FDA is to -- and somewhat arbitrarily make decisions on what they consider is a complicated skin infection. If the cellulitis has to be this big or the patient has to be febrile with the cellulitis or create artificially the group that says, okay, enroll these patients under these guidelines and we will consider that complicated skin infections. And then divide them up into big abscesses or bigger abscesses, ones we consider complicated, the wound infections and the cellulitis, and look at those in buckets as proposed by Dr. Wei. So I think that we have a way forward here that's fairly logical in doing these trials.

DEAN FOLLMANN: The other question had to do with describing the vancomycin studies and their margins, what kinds of infections were they, what was the supportive care etcetera.

RALPH COREY: They were all rather recent trials since 2000 and so I assume the supportive care was about the same as what we give now. We haven't change a whole lot of our supportive care and drainage of abscess techniques, et cetera. So I don't think those have varied a lot. We're mainly looking

 

at tegicycline trials, daptomycin trials.

Obviously, the number -- since 2000, the number of MRSA in all of these trials has gone up dramatically. You look at the linezolid from 2000 which were done in the late 90's very few MRSA. Then you start looking at the tegicycline trials and as I remember it's about 60 to 70 MRSA patients or about14 percent. And you look at the dapto trials about the same, 80 patients about 16 percent. And then you look at the MRSA trials with telavancin and it's about 65 percent. All of sudden it just zoomed. MRSA took off in the United States. So I think there are differences in the trials in terms of pathogens. There's some differences in the trials in terms of percentages of abscesses and cellulitis, etcetera. But I don't think the care itself had varied a lot. Does that help?

DEAN FOLLMANN: Yeah, I was most interested, I guess in the different kinds of infection and relative proportions.

RALPH COREY: I would have to get out a slide and look at exactly what the proportions were, but I would dare to say that the number of abscesses has gone up and amount of cellulitis probably has stayed about stable and wound infections has gone down a little bit.

BARTH RELLER: Dr. Hilton.

 

JOAN HILTON: I would just like expand upon Dr. Follmann's comments. I'm looking at figure 5 of the briefing document provided by industry on telavancin. And for the placebo impetigo studies the cure rates for the six studies range from 2.4 percent to 84.2 percent. And that's almost from zero to one. And I don't think that it's sensible to then take a weighted average of those data and throw away what must be important differences across those studies. I think Professor Wei's proposal of a stratified, weighted average that takes into account of severity of disease or perhaps the bug that infected the patient even though we might not know that at baseline we might know it later and that could inform subsequent studies. And I think it was also in Dr. Wei's presentation that he said that the analysis you don't have to use the information you had a baseline, your not restricted to your baseline analysis. Use the data that you've accrued during the course of the study to help make these weighted averages and do the analysis based on that. Thank you.

GARY KOCH: My understanding is that the six studies that the sponsor used for placebo in uSSSI included the three studies that the FDA presented. And the sponsor included six so as to be more inclusive, because if you're a sponsor and you're less

 

inclusive than you're accused of selecting the studies that you found more attractive. The thing that I tried to point out risk differences the risk differences actually were homogenous across the studies and I ultimately got a slide up to try to show that. And then what I further tried to clarify was that the heterogeneity that you were seeing in the placebo rates could be because in one of the studies patients were evaluated either later in time or by less stringent criteria and that might produce a high rate. And in a different study they may have been evaluated earlier by relatively stringent criteria and that would produce a low rate that would mean that the heterogeneity you were seeing was not random from study to study looking at the same population under the same conditions, but it was simply due to the different conditions which were invoked. And that's why the sponsor thought that within study variability as in a fixed effects analysis was a reasonable way to get a precision. Now they did do a random effect analysis and we showed that as well. The point estimates are about the same, the random effect analysis produces a wider interval. We think the interval is probably too wide because it's mixing whatever random variable there is with the fixed differences that existed from one study to another.

 

We agree that probably the fixed analysis is too narrow. One of them produces an estimator in the vicinity of 20 percent and the other one produces an estimate within the vicinity of 30 some percent. Dr. Hopkins can actually speak to some of the differences among the placebo controlled studies because he did look at those individually. And perhaps he can give some comments about the special features of those placebo controlled studies as a way of shedding light on why one of them may have had very high response rate and the other may have had a very low response rate.

ALAN HOPKINS: Well doing these meta-analysis is always a dicey business and there's always many ways to do them and you're really opening yourself up to criticism no matter how you do it, I'm afraid. But, I noticed that there were two that were extreme. The Eells study reported, I think, 16 of 19 cures and in reading the study they attributed eight of those patients as absolute cures and eight patients who improved. And so I just used the data as it was recorded, but there was, you know, that wasn't clear that other papers did that. And so the other papers reported cures. In the case of the Ruby study where there was no cures, the assessment was done at five days rather than the 7 to 10 days that all the others were done it may have

 

been a little hard to expect that there would be a cure done by day five.

JOAN HILTON: Dr. Reller, may I follow up?

BARTH RELLER: Yes, Dr. Hilton.

GARY KOCH: There was one further point that we could try to share. The data that we showed on vancomycin was relatively homogenous and even homogenous with the telavancin studies and supports that for vancomycin the cure rate is somewhere in the vicinity of 70 to 75 percent depending upon whether you're using a point estimate or a lower confidence limit or how you're getting a lower confidence limit. If one that the placebo cure rate in this condition for these kinds of patients is not any more than 50 percent. We don't have any placebo data for cSSSI, we do have placebo data for uSSSI and we tried to make the best of it to get some sense as to where placebo rates may fall. I think you can rationalize that a 20 percent effect size at a 10 percent margin has plausibility if you also have plausibility for whether the cure rate in these populations for cSSSI is 50 percent or less. If you think it's higher than 50 percent then you indeed can sort thinking about margins that may be more stringent. We think it's probably much lower than 50 percent and we have essentially built in some

 

added caution with the 10 percent margin rather than using a margin that's bigger. But the real bottom line on all of this is that if you accept the fact vancomycin has a cure rate in the vicinity of 70 to 75 percent then to justify a 10 percent margin you have to use whatever insight or judgment or analysis you can do to satisfy yourself that the cure rate on placebo, in this condition, is 50 percent or less using the information that we have on uSSSI and any other insights that you have.

JOAN HILTON: I agree with your approach of using logic and boundaries to set an upper limit on what the placebo response rate could possibly be.

I'm just trying to make the point that in Figure 5 there must be patient variability explaining a good bit of this heterogeneity. It's just -- you know, to to go from 2.5 percent to 85 percent it's just huge. And it seems that some of the studies might be irrelevant to the comparison.

ALAN HOPKINS: Well again it could be patient variability that still would be consistent with the fixed effects analysis because random effects is essentially variability from study to study in the same kind of patient. We could adopt you know the philosophy of the Olympic judges of ice skating or diving and throw out the low one and throw out the high one and use the

 

ones in the middle, we probably would end up with a similar point estimate. We might get a similar estimate of variability. But again we didn't want to do that we wanted to provide the committee with a full range of information that the sponsor was able to locate in their literature search and then let you deliberate with that information.

JOAN HILTON: And I'm just proposing instead of taking a weighted average by either fixed effects or random effects doing more of a apples to apples or to oranges to oranges the way Professor Wei suggested.

GARY KOCH: That would mean trying to sort the patients in each study and into cohorts. I'm not sure how well the references would allow one to do that.

BARTH RELLER: The following is not a law firm, but the order of speakers based on previous hands, Fleming, Goetz and Rex.

THOMAS FLEMING: Well I think if we if we try to get simplistic here and say what is the success rate on the control arm untreated, what's the success rate on vancomycin, what's the complexity and richness that we have to take into account to understand truth. And I gave that -- I referenced back that slide that showed the four studies for linezolid and the

 

differences in success rates were highly, highly different, not explainable by random noise. And when we start looking into factors there are specific factors that have a big influence on success rate. And of course the definition of the end point has a big effect on the overall success rate. But one very positive aspect of the IDSA document was that they did carefully look into a separation between wound erysipelas and abscess. And they found success rates in the control arm of 36, 66 and 76. So we can't talk about whether it's 50 percent. We have to be talking about what the overall context is. And then the treatment effect also varied according to those various subcategories. And if we go back and just learn from the pneumonia experience -- we should learn from other experiences and this committee met on CAMP several months ago and IDSA put forward a document there that appropriately recognized that age was a significant predictor and a significant effect modifier and justified that we could have substantial margins if you were elderly patients or middle aged patient. Well bacteremia wasn't factored in and Fleming and Powers presented before that committee an analysis that looked at bacteremia as well and got a very different picture, i.e., it wasn't just age bacteremia mattered. It didn't matter if you were young. If you had

 

bacteremia, even if you were a young child, there was major benefit from antibiotics which hadn't been factored in the model when they hadn't into consideration bacteremia.

Well we saw a slide near the end of Dr. Spellberg's presentation of this young girl who had major effects. Well, is this an SSI case or is this -- this is specifically a case where the child had pneumonia and bacteremia. We've already established benefit in that setting. We established the Fleming and Powers Analysis that just appeared in Clinical Infectious Disease this past week establishes that anybody of any age with pneumonia and bacteremia gets a major benefit from antibiotics. We already know that. That's not the case we're talking about here. We're talking about cases that aren't pneumonia and bacteremia that are SSSI.

Now specifically what worries me here is while I'm very persuaded that there are many factors that affect what the overall background rate is and what the treatment effect is. We've only be able to drill down on one very important factor and that's the factor of wound infection versus cellulitis versus abscess and that leads to a separate point. My concern is one that the FDA hit on when they talked about major abscesses. And the FDA in reviewing data in their document on

 

pages 20 and 21 said there is evidence suggest that antimicrobial treatments following incision and drainage provide no additional benefit. And the IDSA document here as you recall said this is the area of weakest benefit. Although they tried to justify a seven percent margin, but they had the least amount of data. There was only about 650 patients in total that was included the two trials that the FDA included. And starting some research in this area trying to begin the effort of writing a similar paper in SSSI as we recently published in CAP, Powers and I have been going back to the literature and we've come up with eight studies that have more than a 1,000 patients many of which are randomized trials in major abscesses, that basically strongly reinforce the FDA's insight and concern about what is the level effect in the setting.

Dr. Spellberg said this morning okay we understand, we're left with a very inexact science here that could be seriously flowed by virtue of the fact we don't have randomize comparisons. But there is in major abscesses there is a substantial amount of data. The two FDA studies are the Lara (ph) study that was looking at cutaneous abscess and in 50 patients showed no difference in clinical improvement. And they also had referred to the Rejendrin (ph) study that was looking

 

at 170 patients that showed no difference in clinical cure and that was with cefalexin. Now there's be some issues about whether cefalexin itself may not have shown effect because of MRSA and that's a controversial issue. But there are six other studies that we've come up with that are in several cases randomized trials and some non-randomized trials. There's also natural history data we call it the epidemiology data, and we've hear the the Rue study -- the Rue study referred to several times, but there are five other studies that show that concordant antibiotic versus discordant antibiotics didn't show a difference in major abscess by Fergie (ph), Freedland (ph), Frazey (ph), Lee and Morand (ph), five separate studies. But in addition to that there are these eight studies that are comparative or control trials and I mentioned the two that the FDA had brought up. There are two others that show a positive trend. There are two of these that do show a positive trend. One of them though, the Mirey (ph) study has only 55 patients and the other, a Blick (ph) study has about 80 patients. So in a little over a hundred patients, two studies show positive trends. But the other six involve a thousand patients and they are showing no evidence of a difference on the end points that had been identified. Those other studies include Rutherford in

 

Lancet 1970 that involved 228 patients looking at cloxacilin. Burns in BMJ in 1957 that looked at 59 patients with penicillin resistant organisms that had a shorter time to healing than the 162 patients with penicillin susceptible organisms. Then Anderson had a trial in 320 patients looking at time to primary healing with surgery alone against oral penicillin, against depo-penicillin that showed no difference in time to healing.

Then there was study by McAfee and Harvey that looked at 200 patients with superficial abscesses acute superficial abscesses that showed no difference. I don't know if I named all eight of them, but there's a lot of data here that weren't presented in the IDSA document that are more appropriately controlled studies that are reinforcing the FDA's conclusion that they've already reached or that they've already suggested and that is in major abscesses there's a lot more uncertainty drainage.

BARTH RELLER: Dr. Goetz.

MATTHEW GOETZ: All right. I will follow my law partner newly names. No, but taking a slightly different tact, I find it very difficult to address the first question the yes/no question without addressing the three bullet points that follow because the simple yes/no question does not encompass any of the

 

complexity, as has just been said. As I'm hearing the material that has been presented this morning, reading through the background documents, I come to the clear conclusion that there is a difference in the treatment effect across the various domains. There's going to be a difference in the treatment effect depending upon what the primary end point is defined as being. And there'll certainly be a difference in the treatment effect depending upon the timing of assessment. So in answering the first question yes or no without addressing those other questions first almost seems to me to be putting the cart before the horses in a sense. It's more of a commentary question (ph) than anything else.

BARTH RELLER: Dr. Goetz, this is precisely why we are discussing these points now. And I have stalled on calling the question, because in essence, as pointed out by several speakers, the crux of whether one accepts -- I mean the question is are non-inferiority trials acceptable for the indication of cSSSI, that is dependent upon what ones confidence is that there is a effective antimicrobial over and above all the other components. And so this will come to a question after -- we'll hear further from you now and then Dr. Rex. I wanted to pose a question to our statistician that I think also bears on this.

 

Go ahead.

MATTHEW GOETZ: Right. And, I'm trying illuminate my point here. Is that I was, I guess, suggesting that the discussion that we hold here is, I think, very useful in getting at that point. Because we have to -- we are indeed addressing those three bullets. And I guess my own position is that we might gain traction by asking the issues about non-inferiority trials within separate domains of complicated skin soft tissue infections.

BARTH RELLER: Thank you. Dr. Rex.

JOHN REX: It's fascinating how quickly law firms come and go.

Let me actually pick up on what my law partners had just discussed because I want to get this question to the committee. Can you do non-inferiority for complicated skin? Can you do it in a way that meets Tom Fleming's very vigorous and appropriate challenges? And as a clinician and as a representative of industry, I think the answer is yes, but as Dr. Goetz just said you can't say yes. You've got to say more than that.

What diseases? Well I think that the Spellberg paper has done us a real favor. It has clearly identified major groups for which, if you enroll patients who look reasonably ill or

 