patients who have a disease process in a bad location or patients with a major host defect like diabetes, even if they that can all progress rapidly. And we've all seen patients like that who have scared the daylights out of us because they got way sick very, very quickly. What are the end points you've got to use? Well, we got to deal with this one, are they objective. Be sure about that. Well the things that we look at, you know, I talked earlier about that long conversation that goes on between the patient and the physician resolution of fever, resolution of erythema (ph), resolution of drainage overall clinical care. You actually can define those things and if you look at recent trial designs the wording that's often used is something like well, "complete resolution of signs and symptoms," it's reasonably objective. We may not agree on whether it was today or yesterday that it happened, but if you look over a course of a few days we will all agree on it or not. And speaking of when do we measure it. When do we measure it?

It seems to me like you've really got to go towards the end of course of the therapy that's typically 5 to 10 days, that's not weeks after the two doses -- you know it's not weeks and weeks after the two day point at which the FDA looked at the resolution of fever or resolution of -- cessation of spread.

It's reasonably brief. It's close enough to the real disease that it feels about right. It does capture the key response variables. But what then about the historical evidence of drug effect and consistency, with these different pools, to what extent to ancillary care and permits general medical process and early diagnosis change things? You know, these things must certainly make a difference, but the underlying pathophysiology is the same. And I got back to the Spellberg thing, untreated these are serious illnesses that can progress with stunning repeatedly. We must, I agree entirely, that we're going to have to discount the historical effects to deal with this, we're going to have to. But we should not discount it to zero because there is an effect that we all can get at. And this where I would like to turn to this question of the clinical meaning of what we've got.

The older data really are clinically meaning full and the signals are very, very strong. Now what number can we put on it. And, you know, the number 10 discussed a lot because we have 10 fingers and 10 toes. And as a number it is certainly a lot smaller than the treatment effect for essentially all the meaningful skin infections. But using it a focal point for just a minute not because it's necessarily the right answer, let's

 

think about what it means to do a trial and stay within a 10 percent margin and that's actually the key figure here. Remember, margins are a combination of science and clinical judgment so let's think about what a 10 percent margin means. I have a minimal benchmark that I've sometimes talked about. A math experiment -- a thought experiment. Consider a control therapy that works 90 percent of the time in a study of 250 patients per arm so that's a 500 patients study. You study your new drug versus the old drug. The control hits it 90 percent. Whatever the end point precisely is, is it at five day, seven days, 90 percent. If the new drug is going to have a margin no worst it can actually be, the worst number it can hit is 87 maybe 86.5 lets call it 87. This is the worst case, 87 versus 90 that's a 10 percent margin. It's not 80 versus 90 because that would be a much bigger margin. It's 87 versus 90. It can only be three percent away because the 95 percent CI will be three plus or minus six. You might have to round it up maybe a half percent or so but it's going to rough like -9 to +3 three. That's close enough for me to be -10. I find this to be really helpful, 250 per arm, 90 percent effective by control. In this case I can only measure three percentage points away and still be non-inferior, that's the worse case. Now when you talk about

 

that 10 percent margin it may sound like it's a lot. You know, 10 percent that's big. And Tom Fleming will quickly say, "John, that means that it could be as much as 10 percent worse, right? It could be as much as 10 percent worse." There's actually a 2.5 percent chance that it's more than 10 percent worse. Right? And that's the next thing to think about. Here's your 95 percent confidence interval, there's 2.5 percent to the left; 2.5 to the right. So there's a 2.5 percent chance that it could be worse. Ah, that's the first study. For everything other than -- we do two studies unless it's not the first indication. If it's the fourth indication for a drug and you've seen lots of things else about it, fine, one study. But for the first indication you do two studies. And what happens if both of your studies are within 10 percent? The likelihood that you're really worse than 10 percent is 2.5 squared, or .0006, point 1 percent less than one in a 1,000. With two studies you've actually got a very you have made it unlikely that you're more than 10 percent worse. And indeed you're not even 9.9 or 9.8 percent worse. Think about it for a second. If the cosmic truth is a 10 percent difference your drug is really -- from Dr. Fleming's example, a 70 and the control is really an 80 and you do two studies in a row what's the likelihood you're only going

 

to be a few percent off? It's not that likely. We'd have to do some modeling to figure it out but it's not that much. So the inner margin we're talking about 10 percent is actually pretty good. We base this on our compelling clinically meaningful data. This a huge bit bigger than that and, you know, we're going to have a come up with a problematic solution here. And somewhere in this range is an answer that I think we can justify medically and for which we've got clinical relevant historical data. It's not exactly what you want, but it's not bad. And I'll just close by saying that we've really got to come to a position on this. You the committee, I don't get to vote, I just get to run my mouth for a minute. We've got to decide. We've got to offer the FDA realistic suggestions on how to provide guidance to the industry. We got to help define what complicated means, what uncomplicated means and point at a source of data that says yes there is a big treatment effect and we're going to discount it way back. And maybe you're going to discount it to 10 percent. That's fine if that's what you choose to do. You actually can do it with a lot of competence and I think that's really the thing that I want to say, is that 10 or if you do it in the context of having other approvals for your compound. Thank you.

 

BART RELLER: We have three more speakers, I mean persons, who have raised their hands tucked away and maybe we'll come back to this. There's much expertise around the table and we want to hear from everyone who has something to add, but one of the questions lingering in my mind, we've heard 10 percent figure, we've heard 15 percent. We've seen data on weighting these studies giving the thrust of the IDSA presentation was, I think most around the table belief there are appropriate -- if a non-inferiority trial is acceptable at all what the margins would be would be reasonably different for different kinds of infections.

Is it, from a statistical standpoint, even possible to come up with a weighting scheme without losing something? If our goal is to have a single number is that flawed from the outset or do these things have to be -- and if it can be weighted in coming up with a single number, what is the cost of that in terms of the edges? So we'll come back to that, but first of all in the order of the hands Dr. Leggett, Fleming and Septimus.

JAMES LEGGETT: I'd also be happy to wait because I was going to throw the conversation in a different context after we finish all the number conversation. So I'm happy to wait as

 

long as this is not my only chance, Barth.

BARTH RELLER: I shall not forget Dr. Leggett. Dr. Fleming. As past chairman of this committee, Dr. Leggett will be heard.

THOMAS FLEMING: Well I do believe there are settings in which non-inferiority's can be done. I do believe there settings in which we can come up with margins and I think a 10 percent margin is defensible in settings where you've clearly established major benefit. But just to build a little bit on what Dr. Rex was saying. Most of what he says is, I think, at least in foundation correct. So if you have a 90 percent success rate and you have a 10 percent margin then actually you would declare victory if you had a 4 percent increase, even your estimate was a four percent increase. So you're estimating you have a 40 percent relative increase in failure and that's still a win 90 against 86 is still a win and it's a win based on ruling out that you're 10 percent worse. One though needs to be -- first of all, that 10 percent margin, as we have heard a lot today, has to be based on the fact that you are preserving at least half the effect, taking into account all of these uncertainties about how you are estimating what the effect of your active comparator is. But let's say you've done that. You

 

still in the end and have to able to say it's clinically acceptable to have -- to in fact be up to 10 percent worse. And I always like to turn the tables and say if you had a 20 percent failure rate, an 80 percent success rate with vancomycin or whatever you have and I could come along with something else and I could improve from a 20 percent failure rate to 15 or 10 and it was statistically significant, would you take that to the I mean we heard some discussions about what was presented to us is linezolid superior to vancomycin and the kind of differences you see are 2 to 5 percent. But if you could get that statistically significant, is that in fact enough to say this is important, this is an advance we're reducing the failure rate from 20 percent to 15 or 10? I suspect most people would say yes, particularly if you could reduce it from 20 to 10. Then why is it okay to increase it from 10 to 20? Why is it okay to say this is all right as long as I can rule out -- and the only thing you're saying with confidence is not I'm that you're four percent higher it's not that I'm confident that I'm not more than 10 percent higher just as in superiority if I'm estimated to be six percent better, the only thing I can say with confidence is that I'm at least I'm not the same. So fundamentally, where clinical judgment is really important is,

 

think about this point, non-inferiority is being done because we're persuaded that what we have now is importantly better than nothing so is it to the patient's best interest to give back a substantial amount of that? You better, in fact, have a pretty strong argument that it's much safer to other aspects to motivate why you are so willing to give back. And I want shift gears and just quickly touch on what I thought Dr. Rex, maybe I'm misquoting him, was saying the pathophysiology of this is all the same.

I'm not the expert. You folks, may of you are far more expert than I am, but at least in reading on this I am wondering whether pathophysiology is the same for all SSSI. For example, with skin abscess which is the very place where the clinical data is weakest for showing an effect aren't these bigger abscess, aren't these bigger infections, isn't there a concern about whether we are giving adequate penetration in a skin abscess compared to a cellulitis or a wound infection? Aren't there issues about the fact that there is antibiotic inactivation with lower pH protein binding and bacterial enzymes and abscesses where in fact skin abscesses do have a lower pH? So my understanding is there is, in fact also some pathophysiology that says that the effects of antibiotics might

 

not be the same acrossed all settings. So it's just not the clinical data and I'm asking it as a question, questioning whether we can say pathophysiology is the same. At least the clinical data isn't the same.

JOHN REX: Tom, I was being sloppy. John Rex, I was being imprecise. The pathophysiology over the past 100 years of cellulitis, erysipelas, abscesses and wound infections is a very constant phenomenon. You let them progress it creates the same organisms, it's always been these same organisms. I'm sorry I was imprecise on that. So that actually gives me comfort that the historical data from 1900 are meaningful in 2008.

THOMAS FLEMING: Although in that aspect many other things have changed in terms of supportive care, etcetera. But --

JOHN REX: And that's why discounting is such an important thing --

THOMAS FLEMING: But pathophysiology was something I'm glad you raised because there has been a debate, as I understand, as to whether the pathophysiology differs across types of SSSI.

BARTH RELLER: Dr. Septimus, you're on and you might

 

as an infectious disease clinician also want to comment on your perception of the differences if they are fundamental differences given. I understand what Dr. Rex has emphasized is that cellulitis 50 years ago and a 100 years ago and even before that shares more when cellulitis, quite a part from the different treatment modalities, but that does not mean that the fundamental pathophysiology and some of the issues raised by Dr. Fleming in abscess -- that cellulitis and abscesses are different. Dr. Septimus.

EDWARD SEPTIMUS: It's hard to go after this erudite group to my right. Let me first what I want to say first, I hear a clear consensus around this table regarding trying to classify these conditions by severity trying to see whether differences based on pathogens, obviously MRSA is very different from Group A Strep, that there's clearly differences in subcategory types as the IDSA has so well pointed out, and there's some differences in end points such as the timing of the fever, drainage, size of erythema, etcetera. And it seems one of the things I'm grappling with, and I agree with Dr. Goetz's point before, is that in order to try to interpret these trials we're dealing with such a heterogeneous group where these thing are not as consistent as you'd like to see, it's

 

hard to get my arms around it. And question about whether we should dealing with the bullet points is one of them.

So that was where my point was going to be. As far as the -- I think a lot of things have changed the virulence in the organisms has changed.

The host have changed. People are living longer and they're older. We have much more diabetes in our communities, for a variety of reasons. So I think although some of the basic pathophysiology at the cellular level may have some similarities, I think because of organisms, because of the host, there are a lot of things that are changing. So I think we have to taking that into account and looking at historical controls versus where we are at now.

My last -- it's really a question. What is the bar we want to set for determining efficacy of new drugs in this arena in terms this arena in term so of -- what bar do we want to say this drug is clearly efficacious?

BARTH RELLER: Could our statistical consultants render their perspectives on the fundamental question of whether one can come up with a single margin or whether it must be category specific, quite a part from the definitions of those categories we still have not gotten perfectly clear.

 

DEAN FOLLMANN: You know, I think it has to be category specific basically. And what I'm -- you know, there's a lot of ways to cut up the categories here. And just to try to make things simple. I've been focusing on the different type of infections, from what I've heard and what I've been thinking so far, I think the abscesses are maybe different. And it seems to me that it's possible you could define a size of abscess, where there's equipoise (ph) about whether draining and incision would be sufficient by itself or not. And in that you could do a superiority trial, randomizing draining and incision for -- and placebo versus draining and incision in a comparator. And to me that would be a lot better way to get an answer for an abscesses than a non-inferiority margin where there's, in my mind, a lot of uncertainty about what it would be and so on. I'd be happier making the bridge, you know, from a superiority trial in modest abscesses to major abscesses. I would be happier with that lead than, you know, non-inferiority margin.

EDWARD SEPTIMUS: Well, I forgot to mention, a lot of people divide abscesses into size. If it's greater than four our five centimeters that seems to be somewhat of a relative predictor of a response to I&D.

BARTH RELLER: One of the things mentioned

 

earlier, if one went that route of not accepting a non-inferiority trials for abscesses (still have addressed the major abscesses), but has been pointed out earlier that these abscesses may also be accompanied by cellulitis and bacteremia that then would fall into a different category so that it would require making clear distinctions about definitions of what would fall into a primary emphasis on the cellulitis as opposed to the drainable abscess as opposed to the drainable abscess with a rim of erythema. Dr. Bennett and then Dr. Fleming.

JOHN BENNETT: I hear some general agreement that we need to categorize these patients. But I would like to remind you that the categorization is done by a study nurse filling out a case report form. So this requires making little checks in boxes. So it isn't really the continuing dialogue that Dr. Rex reminds us, between the doctor and the patient, it's the study nurse filling out the case report form that first allows you to categorize the patient and then also determines the outcome. So one of our challenges here is to not only determine the categories, but allow it to be simple enough, clear enough so the study nurse can put it unequivocally into a case report form.

BARTH RELLER: Thank you Dr. Fleming.

 

THOMAS FLEMING: Well Dr. Reller, I think you are on target in your comments about factoring in these co-morbid illnesses and other factors. If a patient has an SSSI and had as the example that was shown by IDSA a pneumonia and bacteremia, there's no question this is clearly an setting where I would do a non-inferiority trial with a 10 percent margin as we discussed back many months ago. That is, in fact, a pneumonia with bacteremia. One of the sponsors, I thought quite wisely, was saying within SSSI, you have wound infections, erysipelas and abscess and ordering them in that fashion. And if a person has an abscess and has a wound infection that person is a wound infection. You would categorize them according to what was most serious. And I approach to the abscesses would be uncomplicated to be doing randomized comparative trials and this is happening. In addition to all the other data that I've been talking about that are in fact completed trials that have been done in the abscess setting there are four major trials that are ongoing or are about to be put in the field. Two by NIAID, one by Baylor College of Medicine and one by St. Louis University. So academia is not waiting for us. They're already launching these trials that are placebo control trials that are looking at

 

bacterium and other interventions that would be used in these settings in uncomplicated abscesses. So this is something already under way.

The last point that was mentioned or the last question that you had raised for the statisticians to address can we do some kind of mixing. And the issue is if you think the answer could be specific to the indication then you really should be looking separately. So let me just simplify the world and say three specific indications, wound erysipelas and major abscesses. So if there are these three settings and you in fact expect that the effect could readily differ in these settings then you probably are well served to be doing studies separately in those indications. Yet if there isn't a strong sense that they would be, it's reasonable to pool, as we do in other settings of the clinical research, to allow us to do studies that are more streamlined. In fact, I think what Dr. Wei put out before today even if you had different margins is it rational to pool there? I think there is some rationality and I'm kind of tipping my hand in the interest of being middle ground here and not highly rigorous, but to be as accommodating without compromising rigor, I could see a justification in spite of all of the uncertainties that we have, in saying in

 

complicated SSSI if your wound or you are cellulitis or erysipelas you could defend a 10 percent margin. While you might think you can defend a bigger margin for wound on clinical relevance I have no sense as to how you would justify that. Well, there you have the same margin so I would think it would be very rational to be doing a trial that would be pooling wound infections and erysipelas and using a 10 percent margin. But if you put major abscess into there, I see no basis for declaring efficacy unless you are using a zero margin, I used superiority for those patients, seems logical to study them separately. But theoretically you could put them in and then do a weighted average, as Dr. Wei was saying, but it just seems more logical that if you could have the same margin for wound infections and erysipelas, that you would put those patients in and do a non-inferiority with 10 percent margin.

BARTH RELLER: Dr. Kaufmann.

CAROL KAUFFMAN: So as a clinician I am sitting here going through the patient's I've in the last few months and trying to figure out can I really put those into little buckets, I think the word was used before, and I can't. Now maybe I'm not such a good clinician, but, you know, I think the patients don't necessarily fall into categories. So you have somebody is

 

they get cellulitis. Or you have the community MRSA person who now comes in with both abscesses and cellulitis. I think they really merge and I guess what Jack was saying, that it's a question of designing right up front where you're going to categorize that patient. I think it is very difficult.

THOMAS FLEMING: We said that, in fact I was following suit with what one of the sponsors was doing. If they had an abscess and have cellulitis that would be categorize as cellulitis. They would be in your trial with a 10 percent non-inferiority margin.

CAROL KAUFFMAN: Well, I think it has to be decided is that true? Is that where it falls. But I think these syndromes overlap. I don't think they're discrete syndromes.

THOMAS FLEMING: It does have to be decided.

BARTH RELLER: Dr. Kauffmann, also they progress so how someone presents and what shape they are in at the time of entering a trial may be different and they can progress, as has been pointed out earlier, quite rapidly. So do you think it's possible to categorize, if not into three preps, two broad categories if one has a predominant effect at the time of entering a trial? For example an abscess that is now accompanied by cellulitis, I mean historically it may have

 

started out as a simpler infection, but by the time they come to your care they've got cellulitis they're an impaired host and you put them in the more serious category. What do you think?

CAROL KAUFFMANN: Again I think it is just very difficult. You could design trials so you have that very much constructed at the front where to put them. But it has to be something that the level study coordinator, as Jack mentioned, that they're going to understand that. And the individual investigator, out in practice as well as in academic medicine, who is going to understand that. And the other issue is imaging and how much you want to bring imaging into this. You may think somebody has cellulitis, but you do imaging and you find out they abscess have an abscess as well. So it gets more complicated as well.

BARTH RELLER: Dr. Rex, Weinstein and then Dr. Hilton.

JOHN REX: The definition thing is really frustrating and if you read the 1992 points to consider and then the 1998 FDA guidance on doing trials and try and look at all the recent trials and try to cook it down, you know, what I come to is that it's actually easier to define uncomplicated than anything else. I can say what doesn't scare me as a clinician,

 

anything else is scary enough that I would put it under the label of complicated because I've seen people go awry when inadequately handled. So what's uncomplicated? Lets try that. A normal host, an acute previously untreated process that's typical of skin, no, zero, zip systemic signs or symptoms so their temp's is not up even a little bit, their white count is not 15,000 and one of the simple entities. What are the simple entities? Impetigo, abscesses that even I would be willing to drain, you know, a little bitty one. Okay. Anything else I location that's the other thing. You know, an abscess on my face bad news, abscess on my hand, that's complicated and then finally I have to say that there's got to be some very diminemus version of cellulitis, you know, something that's not very scary, but these people don't come to the ER. I think that's the other thing about this. This human being has gone to the trouble to get into their car or on the bus and come and wait in line to see me in the emergency room. So they're actually selected out. They're not coming because they've got a little pimple that they'd like me to pop. They're coming because it scared them enough, it hurt them enough that they wanted something done about it. So you start off with somebody who is willing to come and get medical attention. And I think I can

 

describe the people that don't scare me. Everybody else, a diabetic, even with a small process, Dr. Kauffman's shaking her head up and down, yes, those people scare me because I have seen them go downhill in a course of a day because I was, you know, dumb enough not to get serious about it. So it is really a slippery slope with abnormal host. And I think you can define uncomplicated. Everything else even if it looks pretty mild at 2:30 p.m. today is probably in the complicated category and requires -- and actually is the kind of thing in the old days that would take you down. It's the kind of things in the old days that gave you the 11 percent mortality even 20-year-old with erysipelas. It's that kind of process. I'll just throw that out as an observation. Because I think when I think about the collected wisdom of what everything's been published in this era what I have seen personally, what we've been discussing today, if you start with that and say draw a circle around un and now deal with complicated -- there may be milder versions of complicated and there may be milder presentations of complicated more severe presentations of complicated, but ultimately complicated is complicated these are people who can deteriorate quickly. So there's a thought.

THOMAS FLEMING: can we ask for a clarification?

 

BARTH RELLER: Sure.

THOMAS FLEMING: Just a quick clarification from Dr. Rex. You've just defined uncomplicated -- you've just defined uncomplicated, and I thought you just said everything else scares me and it's the kind of thing that used to give us 11 percent mortality. So you're saying everything other than what you just described as uncomplicated scares you and would be 11 percent mortality including the major abscesses that have been studied now repeatedly in controlled trials with questionable differences relative to just incision and drainage, those are 11 percent mortality?

JOHN REX: I'm sorry I forgot to take up specifically major abscesses. Let me do that and then I'll come back to what scares me.

THOMAS FLEMING: All right, so if you simply check off and say major abscesses are different then I'm happy to go on.

JOHN REX: Well, but the thing I wanted to say wat I think that you must be very careful to distinguish minor superficial abscesses, which is what I understand to be the subject of these placebo controlled trials, and you can correct

 

me if I'm wrong, but they are studying people with no -- who fit otherwise into my uncomplicated category, they have a mild process. Now please correct me if I am wrong, but a major abscess that's associated with fever, and those are people who are occasionally bacteremic, and I find it hard to imagine --

THOMAS FLEMING: Well, but your saying sometimes and if you start throwing in things in like bacteremic then of course we have a different world. There are an awful lot of major abscesses that aren't in your definition of uncomplicated that surely wouldn't be 11 percent mortality.

JOHN REX: But staring at the patient I don't know, and that's actually the difficulty with it. Is that as a clinician, you know, you learn ultimately you can't always predict how it's going to work out and staph aureus is the scariest thing that one deals with routinely as a clinician. It's an organism that can take a healthy human being and do them in the space of 48 hours. It's an impressive bug. You know in a big abscess, deep, yes I'm going to drain it. Yes, I know that makes a big difference, but some of the time those folks are bacteremic and just looking at them, you know, I can make a guess, but I'm no soothsayer, I don't know for sure. And I do

 

know that I need to -- but, you know, you should ask the other clinicians going around the table, I mean --

BARTH RELLER: I need to invoke the skills of the NPR interviewers. Dr. Weinstein and Hilton and Goetz.

MELVIN WEINSTEIN: Well I support a lot of what Dr. Rex is saying, but I think part of what we're struggling here is still the definition of complicated and uncomplicated. And I think complicated is more than just as Ed said earlier, deeper infections and those that require surgical intervention. I mean cellulitis in somebody with morbid obesity or peripheral vascular disease or lymphatic obstruction or other immuno-compromise, I mean, that's complicated infection and that's going to require more aggressive approach, but I think the other issue here is we need better definitions. I think the people who are conducting this studies in industry are going to need better definitions so that they can enter patients appropriately in these clinical trials.

BARTH RELLER: This is a great challenge. It's apparent to everyone here the subtleties and complexities of clinical medicine and reducing that to a study sheet that's reproducible is a huge challenge. Dr. Hilton.

JOAN HILTON: I just have one follow-up comment to

 

Dr. Fleming's comment a few minutes back that you would be willing to give up 10 percent efficacy. And I just wanted to remind all of us that that's almost a worse case scenario, so that's our boundary. And the mean is not 10 percent lost of efficacy, the mean is less lost of efficacy than that.

BARTH RELLER. Dr. Goetz.

MATTHEW GOETZ: As we think about uncomplicated versus complicated skin and soft tissue infections, I think it's important to differential between that which we would do as clinicians, taking care of individual patients, where the boundaries may exist in one place and where the boundaries might exist for the purposes of going clinical studies where we want to have homogeneity, relatively speaking, in the patients we enroll. And it may be that not every patient enrolled in a clinical study because some categories -- some patients aren't categorizable as clearly uncomplicated or complicated. And no matter which category we put those patients if we put too many patients on the border in the wrong category we will dilute out the power of our studies. So I think -- I propose that we consider that what we define for the purposes of drug studies be different then how we would approach individual patients in our practice for management.

 

BARTH RELLER: Thank you. Now before we, I think we're approaching the time where we the the question and we can implify on the subcomponents thereof. Dr. Cox, how do we vote yes or no if we do not wish to have -- if we believe non-inferiority trials are acceptable for some indications but not all indications.

ALAN COX: Yeah, we put the bullet points in for exactly this point recognizing that, you know, somebody who answer yes, I mean they're answering yes for a specific patient population. So perhaps the way to go through this would be the vote but when voting having in mind which groups of patients you're specifically referring to, which and points, what time you would assess it. So in essence you would describe the scenario where you think yes is appropriate. It would probably also be fine for folks then to also -- in addition if there certain groups that they don't think should be included, to specifically enumerate that too. Does that help? I mean that may getting to the issue of if somebody's saying yes, what in fact they are saying, yes to. And if there are specific groups that would be excluded, just to specifically state, you know, which groups should be excluded. If there's no scenario where somebody feels that a non-inferiority study could be done,

 

well then that could be straightened no.

BARTH RELLER: Thank you. I believe that what the agency wants is that if we delineate these then we would have a yes, if there are one or more situations with cSSSI that would -- where they may be appropriate and then get the proportion. And we'll try to get a sense after the additional discussion of what those categories might be and what the criteria might be. Again the procedure for voting is three options, Yes, no, or abstain. Twenty seconds later we will announce the results and then we'll go into the reasons why. Yes, Mr. Levin?

ARTHUR LEVIN: Sort of just a point of information. Is the question, Dr. Cox, really are non-inferiority trials ever acceptable; isn't that the question? I mean we can't answer it any other way. It seems to me --

ARTHUR LEVIN: -- the question is, are they ever acceptable, yes or no. Because question two is we're really what we've been talking about, about grouping them, extension. So it seems to me that's the question.

EDWARD COX: I think that is fair. It's always difficult to write, you know, a really good question. And we've tried to do that and I think, you know, if there is a scenario where you think a non-inferiority study could be appropriately

 

done and then describe that scenario that could be very helpful information to us. So yeah, essentially the way you're describing it is a fair way to describe the question.

BARTH RELLER: It's time to vote. The lights on your lower panel are blinking. Press the one that you believe is the most appropriate answer, please. Excuse me?

[Off-microphone conversation]

BARTH RELLER: Amazing as it may seem, despite is flashing lights, it will capture what you did once. And we'll have a double check on that because we have the tally of the voting members and we'll add up the yes's, no's and the abstains and we should come up with the same number as the voting members. The voting is complete.

So the committee has recognized there is a role for non-inferiority trials. Lets start this time at the light Dr. Weidermann, do you want to qualify your yes since they are all yes's, if qualifications may be needed.

MELVIN WEIDERMANN: Right. Thank you, Dr. Reller. I'm in the camp that abscesses are different enough that I think we need to separate them out, you know, and I have concerns that non-inferiority may not be appropriate for many cases of abscesses.

 

BART RELLER: I think it would be very useful to get the separations out and then we can come back to the subcomponents. And in part this will supersede, you know, question number two which should be very efficient after this exercise. Dr. Kauffman.

CAROL KAUFFMAN: Yes. I voted yes. I cannot come up with a specific margin and there's all these numbers running around the table, but I think you target something like 10 percent but it's clearly going to depend on the patient population and the end point where you end up, but it's probably in that target range. I think the appropriate end point is a composite score that takes into account several different clinical aspects in terms of whether the patient has truly responded and the timing for that, I think should be either at the end of therapy or a very few days after that certainly not early on during therapy and certainly not several weeks later.

KATHLEEN GUTIERREZ: Okay. I also voted yes and I also think I would try to separate simple abscesses from everything else. And I'm struggling with defining what is simple versus major abscesses and I know there will be more discussion about that. I can't really comment on the margin dependent, antibiotic dependent, all the different factors we've

 

brought up although 10 percent sounds within a reasonable range. Do you want us to comment on the end points also at this point?

BARTH RELLER: Sure.

KATHLEEN GUTIERREZ: I'm a little conflicted on this. I know as a clinician I like to know at about 48 to 72 hours whether I'm seeing an effect in my patients before I decide whether or not I need to add therapy or change therapy. And so I guess I would maybe argue for an earlier end point as an end to therapy end point, if that's at all feasible. So those are my comments.

BARTH RELLER: Thank you.

DEAN FOLLMANN: I voted yes. I thought we should break out abscesses from cellulitis and wound infections thinking maybe abscesses could be done in a superiority trial. Based on the data that the FDA and Theravacin provided I thought, you know, I'm inclined to think a 10 percent margin is acceptable for the wound infections and cellulitis. The appropriate primary end point, I guess, the test of cure that we've been seeing in the more recent studies seems find to me. That's all I have to say.

MELVIN WEINSTEIN: Yeah this is going to start

 

sounding repetitive. I also agree with the breakdown of wounds and cellulitis/erysipelas on the one side and having a less confidence in the issue of abscess because I think the pathophysiology is different. And I think the treatment is often different where abscesses get drained and antibiotic may simply be adjunctive therapy once the drainage takes place.

I concur with the 10 percent margin and like Dr. Gutierrez, I would like to see more than one time end point measurement, maybe 48 to 70 hours and then at the end of therapy.

ARTHUR LEVIN: Obviously, I voted yes, from the tally. I guess I would separate out abscesses. I think the margin of 10 percent would be acceptable. However, I would like to sort of raise an issue which is informed consent process, that conversation between doctor and patient. It seems to me it would be incumbent on the prescriber to inform the patient based on the current evidence there is a possibility of either an average or worse case scenario, that that treatment would actually be less effective than another known treatment. So while I think it's acceptable I think it's acceptable in the context of a disclosure with patients, between the prescribers and their patients. That this is -- we have

 

limitations on our knowledge and to the best of our knowledge this could actually be an inferior treatment. And I'll wait for the rest of the discussion on the rest of the parameters.

BARTH RELLER: Dr. Hilton.

JOAN HILTON: I voted yes and I agree with Dr. Gutierrez, that two time points might be sensible in this setting and with Dr. Follmann's other comments.

ALAN CROSS: I voted yes, but did want to comment on a concern of about at least how we defined non-inferiority trials. We haven't really gone back to the M1 issue and I think based on the evidence we heard in the discussion --I think while IDSA did a heroic job in trying to reviewing the literature, it's so heterogeneous and for all the differences that we saw I think that the concept of having an M1 based on those data, compared to a comparator is not very meaningful. And actually I was impressed with the fact as -- in Dr. Forest's presentation he said since 2000, he pointed out that we do have Phase 3 trials done, seven of them with vancomycin which were within a reasonable spread in terms of efficacy, On the one hand. But then on the other hand, Dr. Fleming pointed out if you look at linezolid there are perhaps

 

some significant differences. I think a way around that is that perhaps there are -- if one were to go back and analyze the different linezolid trials to see how different those buckets are that perhaps the spread would not be as large. So the point is it is possible to do non-inferiority trials. But I think perhaps analyzing the comparators, where we do have good data in reasonably modern performed trials, according to our current standards, may be a better comparison point than the idea of trying to extrapolate some date out of the historical literature. Having said that then, I think it is possible to separate out the different groups and perhaps wound abscesses would fall out separately and I think that may be an an analysis of both the linezolid and vancomycin trials may give us some reasonable modern estimate of what to expect in those different groups.

Also having been on this committee earlier with you, Bart, at one point we did have a discussion about delta drift. And I was concerned that if we did in fact focus on quote "the placebo effect" that we had have a danger of having a very dangerous delta drift. So my preference for going after the vancomycin and linezolid would at least set a floor under future trials. But on the other hand Dr. Rex did point out that if we

 

do 10 percent of 10 percent, you're not going to get down to a very low level quickly in terms of a drift downward in acceptable efficacy. So I think I'll stop here. I do think that the timing of it ought to be at the end of therapy.

BARTH RELLER: Dr. Steckelberg.

JAMES STECKELBERG: Thank you. I agree with the previous comments and just maybe a couple of others from a clinician point of view. I agree with something in the ballpark of a 10 percent Marge but maybe for a different slightly different reason. I think maybe putting on my clinician's hat I'm already convinced that there's either a large or very large effect of antibiotics in most of these situation and it doesn't really matter to me how large that is at this point. What I'm really concerned with is that a non-inferiority issue. And so I have an established treatment that I'm giving patients. And I reasonably certain that a new therapy isn't worse.

And what does reasonably certain mean? To me 10 percent less effective would probably be unacceptable unless there were a major advantage in terms of safety or something else. But a 10 percent margin doesn't mean it's 10 percent less effective because we have to take in -- it's the point estimate, but there are also practical issues about study size for the confidence

 

interval that gets you there. And to me 10 percent is a reasonable compromise that should be doable and yet give me reasonable certainty that this is not inferior to what I'm using now. And I really don't need to be convinced, maybe with the exception of major abscesses, that it has a larger effect relative to placebo. With represent to abscesses, I think that's an area we're probably going to need some more discussion and data. Some of the references are unpublished and so forth. But it's really hard for me to imagine a clinician seeing someone whose a large say MRSA soas abscess in their back, five, six, seven centimeters surgically rained that is not getting to get antibiotic. And I think all of us have seen those patient bacteremic and very ill. It's just, you know, there's some discussion that there's lack of compelling evidence basis for the antibiotic treatment there, but I would also say that there's lack of compelling evidence that's not necessary. So I think we may put that in the parking lot for now.

BARTH RELLER: Dr. Steckelberg's pointing out there's a huge difference where that abscess is, paraspinous (ph) abscess, soas abscess versus something that's readily accessible with a scalpel, to the naked eye. Ms. Thomas?

JEANNINE THOMAS: I think the abscesses should be

 

separated. A 10 percent margin is acceptable. I think full disclosure to patients at all times is vitally important. And the timing of assessment should be within 72 hours.

BARTH RELLER: Dr. Septimus.

EDWARD SEPTIMUS: Good afternoon. No. In answer to the question I believe that 10 percent is probably acceptable but I would include abscesses and I would like to see actually a superiority trial on those. As far as the primary end point is concerned, I think we are talking about two different issues that Dr. Gutierrez brought up. One is response to therapy. So I think a three day response to therapy seems reasonable. And then the end points, what everything talked about, well that would be done at the time of completion of therapy, or a day or two after. In relationship to that, you know, we talked about this this morning, perhaps in response to therapy how fast the patient responds and how fast they get back to work and how fast they get back to productivity might be another parameter we might want to think about as some of these new drugs come on line. I was just thinking about that. So I think that's it.

BARTH RELLER: Dr. Nelson.

LEWIS NELSON: Thank you. I voted yes as well. I think that the concept of the margin has to be figured in light

 

of other issues involving the drug, in particular safety issue, maybe this is something I could have brought up earlier, but just because a drug isn't -- the drugs we're looking at here are not to replace existing drugs, so just because a drug is inferior to an existing drug I'm not sure that is -- I mean it's obviously a bad thing if it was going to replace the drug but if it does cover the infection in a subgroup or a different group of people, perhaps having an inferior profile, as we're going to define it, while it's not ideal might not necessarily be an unacceptable factor And maybe I don't completely understand the issues and clearly I want the drug to be as effective as it can be. So I'm not sure where to put the margin I think the margin has to be relative to a lot of other issues including safety and other drugs that are out there and how the drug is going to be used in practice. Because I really , as I said before I'm a little bit concerned that things we label drugs for here don't necessarily translate into how they're used once they're released into the real world. I feel, you know, as somebody who does see a lot of infectious disease, even tough I'm not an infectious disease specialist, I tend not to follow my patients very carefully in emergency medicine. Sometimes they come back, we bring them back in a day

 

or two to have them checked, so that 48 hour mark is nice. But ultimately it would seem to me that a longer term outcome is loot more important so at the end of therapy perhaps would be a good place to look. Although I would like to see both end points as well. Since when they come back to me I have to make a decision too, whether I'm going to change their antibiotic or add another one or call somebody for help. Yeah, and I think the issue with abscess has to be looked at. But I was under the impression, when we talked about abscesses, we weren't really talking about skin abscesses and we really weren't talking about deep space infections inside the body. So, you know, for skin abscesses things are a little bit easier because for the most part part they do get drained. You know, and most people don't just treat them with antibiotics.

BARTH RELLER: Well again, as has been mentioned earlier, the importance of delineating those criteria in --

TIMOTHY LESAR: I voted yes that non-inferiority trials are acceptable generally. My comments probably echo some of Dr. Nelsons, is that in thinking about how this applied to the real world and what margins -- so the margin, I believe, tells us something about effectiveness not risk benefit. Much less about risk benefit.

 

Again, I think when we assess risk benefit assuming that it's something that showed efficacy it shows, you know, universal benefit, it becomes problematic. I also, in terms of primary end points I think it's important that that's well defined as was mentioned before. The issue of abscesses may consider a margin less than 10 percent if that can't be clearly defined in trials. In other words, you'd have to have a lowest common denominator as an appropriate margin.

In terms of the timing I heard the comment that so many that times of an early end to end point measurement of efficacy is important, simply because that's how people practice. And I think some of the dalbavancin studies were very interesting that you give weekly doses and there's a big difference between a single dose and a dose at day seven (inaudible) whether they were going to get a second dose at day seven or not, but there's a tremendous difference in efficacy rates. So I think that that was very informative.

BARTH RELLER: Dr. Bennett.

JOHN BENNETT: I think-we not only can, but we must have non-infriority trials. We need newer drugs for this category even if they are not superior, they might be cheaper or safer or available orally. There's a rising problem of resistance that's been reported.

 

So yes, we must have non-inferiority trials of this group. I think we need to develop a categorization based on prognostic factors these types of infections so that we can look at different trials and see if they are treating patients with equal severity. In terms of the end point, remember you only get one global end point. So you can't keep evaluating on day 2, 4,10 and 14. I would pick the end of therapy being the global end point. And yes, we can have secondary end points along the way. I think a Delta around 10 percent looks good to me. Let's remember too when we're thinking about other types of difficult to study infections, like diabetic foot infections, that not every infection is amenable to study. And it might just turn out that diabetic foot infections are one of those.

JIM LEGGETT: Jim Leggett --

BARTH RELLER: Dr. Leggett, right.

JIM LEGGETT: Yes, I voted yes, of course. A few comments. One, I think that one of the reasons that I voted that non-inferiority margins are acceptable is because of the historical evidence that I really do think shows the sensitivity to the drug effect. I think there has been constancy over time. And as an aside to that constancy over time, you've got to remember, in talking about people dying from abscesses of this

 

-- none of us have ever followed, hopefully, anybody with staph or strep of death without treating them. So none of us have seen that. So we really do need to rely on that background that Dr. Rex was talking about. I'm not one to argue if it was 11 percent not 11 percent. I've never seen it. But what I would like to point out is a question of a lot of the discussion, to me, forgot the second part of that M2 calculation which was the clinical judgment part of it. And I think while there's a lot of statistical evaluation in M1 evaluation part of it, there's a lot of noise and a lot of how many angels on the head of a pin. We cannot, with our blunt measurements actually get down -- I think if we're talking about of a lot of the discussion, to me, forgot the second part of that M2 calculation which was the clinical judgment part of and I think while there's a lot of noise and a lot of how many angels on the head of a pin. We cannot, with our blunt measurements actually get down -- I think if we're talking about 10 percent margins, we can -- or 5 percent or 15 percent, that's all well and good. But in reality, based on dealing with noisy systems I can't reliably tell the difference between 10 and 12.5 and 15 percent in terms of saying yes to one drug and no to another, because I don't really trust the placebo effect on which we've decided to base

 

all this.

And then upon the end points that change from study to study and all the homogeneity or heterogeneity in between. So I'm a lot less -- we need it from the FDA regulatory standpoint but I think we also have to take it with a big grain of salt and I wouldn't necessarily kick out drug X because it's NI was 10.1 percent in a situation or 15.1 percent if we decided. I also think there's a lot of -- everything touched about the variability of the clinical course. We also have to try to make this as much as we can generalizable to the public. So I think we need to recognize in trying to fill out the boxes that Dr. Bennett was talking about, somebody has to fill out the box, so we need to weigh the fact that lots of people with that abscess also have cellulitis around it, which should automatically, in my mind, kick somebody up to the cellulitis part of it from the abscess part of it.

Historically when the IDSA thing looked at that 14 percent with major abscesses, I'm almost sure that they were only dealing with skin and soft tissue because they didn't have C. T. Scans, MRI scans, they wouldn't have picked up that soas abscess. That person would have died of bactermia. So I think in that very slow margin of -- very low margin for major abscesses

 

we got to remember that we're probably talking about skin and soft tissue structures, very easily palpable. Finally, in terms of end points I think end of therapy makes most sense to me things before then, to me, are mostly surrogate in nature. The end of the favor, the end of the spread, that sort of thing. It has to be a clinical end point, no longer mortally. I would like people to remember that we probably, in looking at these trials are not going to be able to factor in relapses of infection, which is so common as Ms. Thomas pointed out regarding MRSA and how many times you had the infection and it's going to come back. But also on the fact that after somebody has been transient bacteremic from the skin and soft soft tissue infection, a week later, two weeks later they're going to pop up with their septic arthritis or their discitis. Are we going to be able to capture those people? Probably not in this end of trial therapy. And then there's a lag faze for things to come up. And that brings up to mind the whole issue of the wound infection part of this, because you may have infection there but not see it for five to seven days later. I think I'll just shut up there. Thanks.

BARTH RELLER: Dr. Fleming.

THOMAS FLEMING: Well I think there's been a lot of

 

answered this my thought was the question isn't whether we could do non-inferiority but in what manner, how and what setting. Where the clinical setting matters, end point that we choose matters, the nature of the margin, it depends on all of this. So to try to condense a lot of what we've said into a small number of comments, regarding clinical setting, if we are to do non-inferiority it needs to be in a setting where we have sufficiently serious diseases, sufficiently serious conditions that would match what we've seen historically as we've tried to assess the effect of the active comparator. And I agree with comments made before that we really do need better clarification of the definition of uncomplicated verse complicated and we need better clarification of the definition of what's major abscess.

I tend to think of it as subcutaneous abscess. But this needs to be more clearly clarified. And that is important because, I believe to do non-inferiority based on what is currently evidence based, we can but we can in settings of wound and ulcer infections and cellulitis and erysipelas, but not currently based on what we know for major abscess. In terms of the outcome the outcome should be a clinically relevant outcome. It should capture the essence of what patients care about.

 

Caregiver's appropriately used signs and symptoms to judge how to manage a patient, that's fully appropriate. Ultimately the assessment of effect should be based on what is the patient specifically really cares about. So worsening of symptoms, redness, swelling and pain. In IDSA I thought they did a very nice job in categorizing eight categories of elements that would be important tangible failures: death, septic complications, progressive worsening of infection, persistence of lesions for at least 28 days, relapse, recurrence of infection, failure to heal wounds, failure of skin grafts, amputation.

Of course, as we discuss the IDSA document correctly pointed out you change that end point and you change the margin that you're able to justify. So the end point does need to be clinical relevant. And ideally should have these components that were just noted. In terms of timing this is a tough issue. We want to be inconclusive and yet we want to have sensitivity. The end point has to be chosen at a time where we have historical data that that points out that we have benefit. And the Snodgrass papers, which are two of the important ones that FDA was using the show benefit, those were assessment at two days. So my own sense about this is the optimal times is probably 10 to 14 days after initiation of therapy in order to

have fairly comprehensive assessment of what we're doing, and yet to still be able to capture the essence of a treatment induced effect verse a natural history resolution. There's no data to base a margin if you use a later point in time. The data that we have aren't establishing a margin if you use test of cure as the time period for assessing. Historical study show that there is - and for most of these infections, a high level of resolution later in time. But I do support the interest in looking later in time. later in time for a supportive measure makes sense. Or, if we wanted to do a superiority trial then I'm perfectly comfortable with later in time for a superiority trial. My concern is using a later point in time for non-inferiority where had that very nice example that FDA was showing earlier on where we were looking at prevention of increase in lesion size. And if you looked at two days, four days you were seeing a difference. If you looked out past then you were not seeing a difficult of the antibiotic.

The issue of margin is obviously a highly challenging issue. I think there are a number of features that go into this we are are doing non-inferiority we accept that antibiotics work in the setting in which we're doing

 

non-inferiority. And I believe we've established antibiotics play an important role in providing benefit in wound infections and erysipelas. And therefore you because we have important benefit and it wouldn't be appropriate to do a placebo controlled trial, it equally isn't appropriate to lose a significant amount of that efficacy. So it's not purely arbitrary that people have forward with the idea that you've got to preserve at least half the effect. And while people have said it's arbitrary, it could be less, well that same arbitrariness means it could also be more. How much of the effect is someone willing to give up. And Dr. Levin, I think, nicely pointed out there's an ethical issue here too, you're randomizing against an established intervention against an experimental intervention that actually you're hoping is the same, and you're trying to rule out is worse. It's an interesting informed consent.

And in fact there was an article in 2007 that challenged the ethics of doing this. I think it is acceptable ethically, but it certainly, as Dr. Levin pointed out, it's something that informed consent as to address. And the clinically relevant loss of effect needs to be factored in. This is a critically important -- this is not statistics this is clinical judgment from the prospective what the patient really

 

cares about antibiotic that we have as our active comparator are we willing to give up.

And I think it was nicely pointed out earlier, by Dr. Paganini, that we have to factor in safety as well And if we in fact anticipate that we are safer that gives me a greater comfort zone with using a 10 percent margin. If we in fact though anticipate safety risks, I really struggle with the justification of a margin of 10 percent. And one other aspect in thinking about the margin is we need to choose an active comparator from among those that have the best evidence for benefit. There are multiple choices of active comparators. And we don't have great scientific, evidence-based medicine to compare them but we do have some evidence. And I think somebody was talking earlier about what we often call bio-creep (ph). We have studied antibiotic in this setting by repeatedly looking at non-inferiority trials on top of non-inferiority trials on top of non-inferiority trials. And what bio-creep means is eventually after two or three generations, while maybe you're only losing a little bit of efficacy each time, that can compile. Well it's less likely to compile if you're really careful to try to bring would, as the active comparator, the regiment for which there's the best

 

evidence of benefit. That's just ethical that's just good clinical practice to offer patients what we think is in their best interest. And it also can help to diminish the bio-creep. So context where one takes all these factors into account, preserving a substantial fraction of the effect making sure that what we are looking at isn't giving up what patients care about as clinically relevant loss of effect, where we factor in the safety profile, where we are choosing active comparators that are among the most effective, with all of those things I'm persuaded we can do non-inferiority

and I think the margin could be as great as 10 percent

But that is in a setting where you're not including major abscess. I don't see that we can conclude benefit unless, in a major abscess setting we're actually showing superiority.

And in the last issue, and it's really somewhat related to the first thing I said about clinical setting, one of the concerns I have is when we look at the IDSA document, we were discussing this in the Q&A that occurred earlier, we're looking at penicillin at a pretty pristine point time. And the IDSA pointed out, by their own words, "antimicrobial agents continually lose efficacy over time." And Dr. Spellberg's response to my concern about that, that we in fact might be

 

overestimating vancomycin's in our non-inferiority trial by estimating penicillin's effect in a pristine time of lack of resistance, was we're going to make sure no one on our trial has resistance to the active comparator. So if that is your justification for a margin as large as 10 percent, then we need to do that. We need to make sure. Now some people might say, "But Fleming, you're leaving out the very patients we can best benefit those that have VRE, but those patients have minimal benefit from vancomycin." Well I don't want to leave them out. If a patient has resistance to anything that we have then I would put them in and do superiority, because if what we have is no longer effective against a given person's infection, we don't want to leave those patients out but we don't do non-inferiority to establish their effect we do superiority. So I don't want to leave those patients but out if we're including them then it's got to be superiority.

BARTH RELLER: Dr. Goetz.

MATTHEW GOETZ: All right, many of my points have been discussed, not surprisingly. I did vote yes. I believe that major abscesses need to -- that minor abscesses need to be considered in a different category and we do need to pay some attention as to what the the

 

non-inferiority limits should be for major abscess. It may be different than it is for the other categories where I'm persuaded that 10 percent is likely to be correct. In terms of the timing for the primary end point, I believe that is the end other have talked about safety being an important consideration in establishing where the non-inferiority limit might be set for a particular agent, I think it's also critically to look at where the antimicrobial advantages of the new agent might be. While we continue to have very effective agents for Group A streptococci, there's really been no resistance, no emergence of resistance to beta-lactams, clearly we're in a very different domain with our methacillin resistance staph aureus, where we have considerable concerns about the creeping emergence of resistance to vancomycin. So were there to be an agent coming along that offered potent activity against MRSA just as we consider potentially having a more narrow limit for M1, if there's toxicity issue, we might consider a little bit of wavering there if we have potential hopes for much greater activity as to pathogen which I believe is of far greater concern than the streptococci.

BARTH RELLER: Thank you. Dr. Alston.

KEMPER ALSTON: I guess at the end here I would

 

comment on something that I don't think has really been stressed today which is the design and conduct of the studies. And it just seems to me when you're doing non-inferiority trials that you're encouraging mediocrity and lack of attention to detail. And it strikes me that we see patients who have been pretreated before enrollment. We see patients getting active drugs during study, we see some people getting surgery some people aren't, it's it's hard to tell who. And all of that obviously is a recipe that all of the patients are all going to turn out the same way. And obviously encouraged in this study design. And I just think that -- and I'm not a statistician, but I have no idea why we would look at this dataas intent to treat. As clinicians we accustomed to looking at superiority trials and we hinder superiority trials by looking at intent to treat and that's fine. But it seems like we have to fiercely look at those who actually were treated per protocol. And I would even argue to over enroll and really throw all those out who violated the protocol. And really ask you're are these drugs something other than equivalent. and I think we're so accustomed to looking at superiority that this is really a huge shift for us. I wonder how many these trials have really shown inferiority or in fact superiority. And I would suspect that most of them show

 

non-inferiority because of the way they are set up.

BARTH RELLER: Dr. Katona.

PETER KATONA: I voted yes it's hard to be origin when you're at the very end here, but I'll try you know, we've talked about abscesses and that they might be going into a different category. But I just wonder --abscesses are not all the same, even large abscesses, I mean some of them are multi-lockular (ph) some of them have to be drained multiple times, you know, in addition to their location and size which has been talked about already. They're recognized at different times in the course of a patient's illness. So I'm not quite confident where they will actually fit in the whole scheme of can't pin down a number very well. I mean we have one drug that's being looked at in this meet which came up with 10 and 15 percent in two different trials for example. And you know, so can you have really something that's quantified that's based on a compounding of all kinds of quantities? I mean you're talking about what the effect of a placebo is, what the effect of a comparator is, you know, what the educate of a compare TOR is, you know, what the Y definitions that are involved here, the methodologies being different. And you take that whole number and then you arbitrarily say 50 percent of that.

 

So to me there's a lot of ambiguity there, so it's very hard for me to pin that down to a number. So can you have a range? Well if you have a range then the people will take whatever is most advantageous in that range so you really can't do a range. But can you have a sliding scale, for example, that might work a little bit better. I mean do you take into account safety conditions, as Dr. Fleming said, if something is really, really safe do you give it a little more leeway when it comes to a non-inferiority margin for example, would be something to consider.

And my last point has to do with a historical perspective. When you look at the IDSA analysis, which I think was done very well you're talking a time we were using penicillin and now the bugs are different, the drugs are different, the people are different, the imaging is different, the supportive care is different. How accurate is that going to be. I mean we know that antibiotics help but to quantify it that way that they have, to a specific number is little bit more troubling and difficult for me to appreciate. And now I could understand how maybe wound infections might get more play than major abscesses do (inaudible) put that into a qualitative rather than a quantitative way. But it's hard for me to kind of

 

go with these numbers to say, well this is based on this historical data, we should use seven percent for major abscesses. Those are my comments.

BATH RELLER: One of the difficulties we face, and this has been mentioned earlier is the need for doing clinical trials and to encourage clinical trials is to have a reasonable target that is adequately defined and not have shifting ground during the conduct or certainly after completion of the trial. Therefore I think the 10 percent is is a reasonable balance between wanting a defined target and recognition of the reality that the effectiveness of penicillin when there was no penicillinase (ph), no MEC-A (ph) and vancomycin and or linezolid or other compounds with the mechanisms of resistance that we are now aware of are different margins of efficacy. And consequently the less the antibiotic effect, the smaller the margin. Consequently, 10 percent, it's lower than the 14 and the 20 percent -- 21 percent of IDSA, but it seems to me entirely appropriate given all of the things that have been mentioned about changing patients and changing organisms. Clinical end points, I think

 

standpoint, up improving on therapy is important so somewhere out two, three, four days out into it, where as Dr. Septimus pointed out, there's there's decisions that are being made to continue or not continue, completion of therapy and some reasonable timeframe afterwards to pick up the relapses. One of the things that these drugs -- the newer drugs and the newer organisms, I think do more so than in the past is they come back grieve the patient and their provider. So I think that assessment at multiple points, on a clinical basis is important. And the 10 percent, if one is going to have a single figure it's imperative that there be as much homogeneity as possible, the definitions as strict as possible, as Dr. Alston has pointed out, so that we don't lose something in the process with the utilization of non-inferiority trials for the ethical and other reasons of getting patient to enroll in these studies.

So Dr. Cox I think there's a clear prospective of the committee, some wider range, but that cutaneous -- subcutaneous abscesses that are palpable, visible and drainable should not dilute the rigor of a non-inferiority trial with regard to the more serious complicated infections that would fall in the category of cellulitis, erysipelas and wound

 

infections.

Lets shift to question two.

Now in recognition of the size of the group and physiologic, realities I would like to suggest that rather than everyone exiting, I mean we're sort of in a dilemma, everyone can exist for a 10 or 15 minute break but we may not finish by five o'clock. So what I would like to suggest if there be no judgment involved, if anyone needs to take a brief break just take it and get back and enter the discussion discussion is not evenescent, it continue on, it will be extensive and it will be importantly somewhat duplicative.

Question two is up for discussion before we vote. In question two, "Please discuss if it is justify a non-inferiority margin complicated SSI as a group or should it be justified by specific type of infection"? we can have complete splitting or some degree of lumping discussion.

THOMAS FLEMMING: Clarification? So there are three parts to this question. Haven't we answered the first part? We all -- because it was so integral to the first question hasn't that already been answered?

BARTH RELLER: I think it has.

EDWARD COX: Dr. Reller, yes and I think we've heard

 

a number of comments that are, you know, relevant to the same types of things that we're asking in question two. If there were additional comments or however you'd like to proceed. But I think we have heard information that is helpful to our --

THOMAS FLEMMING: So it's the third component though is -- the third component is something beyond what we've discussed, I think, the foot --

BARTH RELLER: And also some aspects of the second more appropriate superiority trials in -- the more superficial abscesses that are accompanied by drainage is the division between wound infections and cellulitis -- should there be some balancing there if one is going to have a single margin of 10 percent? Dr. Rex.

JOHN REX: Two comments. One is that to answer that specific question you would need to have a mixture of the two in your trial in order to get the broad label of activity for complication skin infections. And you can't just have five percent of one and 95 of the other, that would -- but I think they would have the same margin mainly because the true effect size is much, much bigger and 10 percent is what the group has discussed as being the least amount of deviation from

 

the active control that any of us or willing to tolerate

BARTH RELLER: would you like to suggest boundaries of 30/70, 40/60?

JOHN REX; You know, it would -- if all you're including are cellulitis and wound infections, then you know, 30/70 maybe. But let me actually -- I want to back up one step and say something about distinguishing these things on the fly. Wound infection is pretty clear but when you get into cellulitis with and without abscess and sometimes you come in and image it and you discover there's a little pocket of what looks like something a bit deeper is that -- is that now out because it's an abscess? I want to make a plea about abscesses that we be very careful. We've used the term major abscess I think kind of in a sloppy way so far. Because sometimes we say, well if I can feel it that's okay, but are you really talking about things like maybe in the arm or some really nonthreatening location? But if it's on the side of your head, you know, going up into the ear, that's quite palpable but not something that I would treat as a minor process, because of it's threat to major structures. So I think it's important -- and then we talk about soas abscess, but deep abscesses.

I think there's an approach to abscess that needs

 

distinguish -- and we struggle for words, and I'm not sure what the best ones are, we need to distinguish really relatively safe looking, nonthreatening location, healthy host, no fever, abscesses from deeper, scary spot, bad host abscesses and be careful that we've not lost the fact that the later category probably does have a real treatment effect. And so I feel like the three things can be harder to distinguish on the fly than we give credit for. So I would run them together, I'd give them a ten percent margin, because I think that's less than the real effect.

BART RELLER: Dr. Kauffman.

CAROL KAUFFMAN: Yeah, I would agree. I don't we've defined what a major abscess is. I mean I can think of something that is palpable, which actually is an abscess in the poroti (ph) gland. Or you see a carbuncle on a diabetic's neck, clearly palpable, you're clearly going to drain it, everybody is think NIH study, for example that's ongoing is little ditzels that you feel comfortable just draining but I don't we've come up with a good definition for the FDA.

BART RELLER: Anyone willing to make some further stabs at what -- in language that could be put into a protocol? Dr. Goetz.

 

MATTHEW GOETZ: Well I think we've touched on it before but the presence of fever, I guess I can give it a number, call it 101 degrees for point of reference. When we talk about a white count greater than 15,000. We can talk about critical anatomical locations. I think the head and neck locations, in -- head and neck locations go a long way to that. Now it gets a little combinatorial and it's the ands and the ors that get us into problems with making up a case report form which can be easily used by our clinic nurse. But I think those are many of the essential definitions. Perhaps the perineum as well, deep seated abscesses in the perineum as being another site for complicated abscess that frankly in any clinical practice I would routinely give antibiotics as well as making sure there was adequate surgical drainage.

BARTH RELLER: Dr. Leggett.

MATTHEW GOETZ: The size of the question that I heard my personal perspective is that size is less than important than the physiological consequences of that, expect perhaps if we start to operationalize in the perineum, than size may be important, you can get a small buttocks abscess that maybe doesn't always require drainage, so five centimeters would

 

be a place where I'd draw the line, because it's been used other places. But I certainly But I certainly can't call that a validated prognostic indicator.

BARTH RELLER: Dr. Leggett.

JAMES LEGGETT: To follow up on Matt's point about the size, we got into is size thing because that's what antibiotics can defuse into and that's about two centimeters so that we treat -- when we can't open it up we give antibiotics and it defuses in about two centimeters. But other than that I don't know of any data that the size makes any importance. I mean I'd worry about a two centimeter labia major abscess or a Para-rectal abscess of two centimeters as much as I would worry -- more than I worry about a ten centimeter abscess on would worry about a ten centimeter abscess on somebody's thigh. I mean, so that the critical anatomical sites which I would also include glutial, right by a joint or on the face those kind of things have to be rules into this. But I don't think size per se is as important the surrounding rim of erythema and cellulitis that goes along with that abscess that you can't really based on just the size of the abscess.

BARTH RELLER: Septimus.

EDWARD SEPTIMUS: I probably didn't make

 

myself clear. I don't think size in and of itself should be a criteria. Be in separating ones that are more complicated, without some of the other things that etcetera, that may be one of the elements to consider in making it complicated, if it doesn't have some of the other elements that you mentioned. That's what I meant to say.

BARTH RELLER: Dr. Fleming.

THOMAS FLEMMING: Well certainly if it does Have other elements, if it has elements that are wound infection or cellulitis or erysipelas, than certainly they already fall into the other categories we talked about. There are many studies that exist that have looked at incision and drainage and antibiotics added to an abscess that can be managed with incision and drainage is the area of uncertainty. So there's evidence here and that evidence needs to be more carefully examined by the agency before one would be, as the committee indicated, before one would be doing non-inferiority trials with major abscess or I call a subcutaneous abscess patients included for the 10 percent margin.

So we were talking about the issue of the 30/70 or 40/60 or whatever you were defining. And it certainly would be important if you're were going to allow a single trial I think

 

it's rational to do so, a single trial to study non-inferiority for an antibiotic in a setting where you have wound infections or cellulitis, erysipelas. If there is a sense of uncertainty as to whether the effects apply equally in those settings, that would argue for having an adequate representation of both. So it really comes down what somewhat to a very difficult question and that is, how likely is it that the intervention's effect would differ in a wound infection from cellulitis. And your not powering the trial typically to each group but you want to know that the study gives you a representative sample so that if the approval is given to both groups there's a basis to do so.

BARTH RELLER: Dr. Goetz.

MATTHEW GOETZ: Just in response to that question, I think that part of the answer is that there is some expected difference in response because although certainly Group A streptococc both domain, the relative distribution of pathogens, causing cellulitis and wound infections differ. We expect to see a higher proportion hire proportion of beta-hymeletic streptococci in patients with cellulitis or erysipelas and a higher proposition of patients with staph aureus and the wound infections. Certainly those rules aren't pure, but they are

 

general principles that we still observe epidemiologically and our relative effectiveness to antibiotics may differ across those two groups of pathogens.

BARTH RELLER: Recognizing on their absolute numbers, but their relative numbers, coming back to the IDSA presentation the cellulitis -- the 14 number that was mentioned and the wound ulcer 21 percent, and I'm translating that into relative rule of antibiotics with all the caveats that have been mentioned, for someone who's mathematically statistically talented, did those two numbers give you a sense of what the boundaries should be? For example, no fewer than -- or no more than -- no fewer than 25 percent in either of the two categories, or 40 percent? Can one draw any sort inferences for what would be a good 14,21 not the absolute number? Dr. Rex.

JOHN REX: I don't claim vast mathematical talent. But one thing you could work back into this is to say what does it mean in terms of actual number of cases of each flavor. Just as a thought experiment, let's pretend we do a 400 patient trial, because that would divide easily. A fourth of that would be a hundred and two arms, that means you would have 50 on each drug and 50 of each drug means the granule -- or one person cha ge up or down is two percent change. So that sort of feels like

that's enough granularity that 50 is the denominator that feels kind of okay. If the denominator was only 25 in a group I might be kind of cranky. So, you know, something like 25 percent of each of the groups just has a quantitative feel you're not trying to power it but it's enough to give you a sense of being able to at least look at that group and you wouldn't say well that's too small to be even analyzable at all. You might start with just a practical analysis like that.

BARTH RELLER: Dr. Bennett.

JOHN BENNETT: Let's remember that once a drug is approved for skin and soft tissue infection that the majority of use will be for more severe infections. Every study has been shown that most drugs are used for off label indications so when we put our mind to having a barrier to what degree of confident should we have that this for drug should be marketed for this indication? Let's not forget that it'll be often used in fact maybe even more commonly for more severe infections.

BARTH RELLER: Let's tackle part three here.

That has got relatively -- some attention but not sufficient. Should patients with diabetic foot infections be studied in a separate clinical trial or should they be included cSSSI trials? Dr. Kauffman.

CAROL KAUFFMAN: I think it's a different beast and would require extensive imagining study to make sure you don't have osteo-myolitis underlying. And the treatment would then be different. And I think they're best serve by studying them a separate entity and not included in the others.

BARTH RELLER: Dr. Katona and then Dr. Alston.

PETER KATONA: I agree with Dr. Kauffman. You know, they have a completely different epidemiology. I mean the whole epidemiology of it is different, the microbiology is different. They have other circulation issues that have to be addressed. The overlap between cellulitis and wounds also have to be considered compliance comes into it, accessibility to good wound care comes into it. So in my view it's a completely different entity that should be looked separately looked at.

KEMPER ALSTON: Yeah, I agree. I handle them separately because the chronic ones have bone involvement and the acute ones -- it's not a reliable history because of their neuropathy. And even the expensive radiology is totally unreliable with a sharco (ph) foot. So I would conduct trials separately for diabetic foot infections.

BARTH RELLER: During Dr. Alston's comments

 

Dr. Septimus was shaking his head in concurrence.

BARTH RELLER: So how important guidance is it to delineate the category of diabetic patients with foot infections at high-risk for osteo-myolitis in patients who have diabetes not accompanied by micro vascular injury neuropathy, etcetera, least at the time of their current infection, not saying what would happen down the road. Dr. Leggett.

JAMES LEGGETT: Yeah I was going to play devil's advocate about this diabetic foot thing. Because look at our epidemic of obesity, okay how are we going to define diabetes, look at the number of people who have then have peripheral vascular disease, who don't have diabetes but have the chronic ulcers.

I note that in the FDA's thing they had wounds/ulcer, okay. So then most of those ulcers were presumably diabetics or something that we're basing our non-inferiority margin on on those past data. Also if we want this to be generalizable, and as Dr. Bennett pointed out, the drugs are going to being used in other situations, I would like to have some diabetes in our skin and soft tissue infection group upon which to have a better idea of who we're actually treating once the drugs come on the market. So I would sort just play devil's advocate and say yes, we ought

 

to throw those people in. We would worry about how we're going to figure out whether they have osteo-myolitis or not later. But I wouldn't throw out diabetic foot infection unless by that you have another diagnosis that excludes it from skin and soft tissue infection because I can't deny that there's skin and soft tissue infection in a diabetic who has a foot.

BARTH RELLER: Dr. Cross.

ALAN CROSS: I think that perhaps may be true, but from a practical point of view assuming that there's a finite number of people who might be entered into a clinical trial, it seems that we already have an interesting mixture between cellulitis, wound infection and abscesses. And we then start to add in the diabetic foot, we're going to enter into a more difficult realm of do we limit the amount of each category in that overall group. Because we can easily dilute out, at any one center, I might add, the number of diabetic foot infections.

So I think in practical terms, it would be difficult to include them overall and for the reasons mentioned. I think there's more than an ample number of patients with diabetic foot infections that we could do a separate study in them and at least have a more homogeneous baseline from which to make comparisons

 

BARTH RELLER: So is it -- do diabetes and obesity and what everyone comes quickly to mind of diabetic foot infections are clinically different entities with different prognosis. So is it possible to define what would not exclude including in a cSSSI based on having diabetes or etcetera, but not having evidence of impaired neurological or vascular function such that it becomes such an impairment? I mean what I think Dr. Kauffman was alluding to and Dr. Katona and Alston quickly reiterated. So can it be defined such that it enables some to be included in the general category and others to have specific indications and ancillary therapy for them? Dr. Kauffman.

CAROL KAUFFMAN: Well I think one simple way to approach that would be plantar pressure ulcers to have those as a separate category. That's the diabetic ulcer to me. So a diabetic who happens to have cellulitis on their shin could be included in the study, but it's the pressure ulcers that I think we treat very differently.

BARTH RELLER: Dr. Alston, Dr. Katona do you -- would that be an acceptable delineation?

KEMPER ALSON: Well, you know, you were talking about complicated and uncomplicated SSSIs, you kind of have to pick

 

the uncomplicated diabetic foot ulcer into the complicated SSSI category, which would make it a little cumbersome and a little difficult to work with. Because once you get into the complications of it, then again it brings up these whole new categories that I mentioned.

MALE VOICE2: Dr. Steckelberg and then Dr. Goetz.

JAMES STECKELBERG: I would just add to that you know, in the diabetic foot a lot of those infections do involve abscesses as well within the foot. And there are neuropathic sharco feet that are more than pressure ulcers. There are non-healing amputation sites and a whole variety of things which just are simply a different disease process.

You could, as you're suggesting, include sort of what looked like ordinary cellulitis in diabetic patients who have normal TCP-02s or normal vascular supply and normal neurologic findings. But I'm not sure the juice would be worth the squeeze in terms of the proportion of diabetic patients that have that kind of infection relative to the rest of the accrual in a study.

BARTH RELLER: On the other hand, would you want to obviscate the effectiveness of therapies for what Dr. Kauffman was describing by patients who had diabetes and cellulitis

 

without the vascular and neurological sequelly (ph)?

JAMES STECKELBERGB: I think that's a very valid question. And on the other hand, if I had my druthers I'd rather have a well designed study in the diabetic foot infection.

BARTH RELLER: Dr. Goetz.

MATTHEW GOETZ: I think that Dr. Kauffman' suggestion about excluding people with plantar ulcers and to try exclude people who had gas and soft tissue is another obvious severe complication to the diabetic foot infection, there might be a workable solution in this regard.

BARTH RELLER: Dr. Rex.

JOHN REX: So what we're talking about is the difference between diabetic with an infection and this entity that gets its own textbook chapter called diabetic foot infection, right? And we might need to spend a little time looking at what some of the recent trials have done. I just did a very slight sidebar. And an idea to think about is the -- what is worthy of study would be an acute, probably gram-positive infection, even if it's in a foot, even if it's in a diabetic. The thing that we're trying to not study -- or the thing that we're -- or rather, I'm sorry, the thing that we're

 

trying to say is really, really different are the more chronic infections of the foot and perhaps neuropathy.

I don't know how much neuropathy figures into it. But what you want to do is look for an acute infection that can then conceivably resolve as opposed to a chronic one that involves (inaudible). Now I know full well that sometimes you see an acute infection and it turns out that it had gone quickly to osteo. So it's a slippery slope here.

But I do think it's important to incident diabetics. You know, we're going to want that trial experience with our drugs. And so to say that all diabetics with lower extremity infections are out, I wouldn't want to do that. And maybe it's something about polymicrobial ideology as well that figures into this. We probably need to spend a little time chewing on this before it gets nailed down.

I think it is slippery, but you don't want to exclude such a major part of it, because how much of diabetes is diabetes? That's the other thing, you're talking about the obese patient with some glucose intolerance.

BARTH RELLER: Dr. Alston.

KEMPER ALSTON: You know, the other thing to come to mind is that the true diabetic foot infections that we're

 

talking about are by definition typically polymicrobial. And since we're, in this example, studying gram-positive drugs, we're going to have to use other drugs. And it just seems such a muddy category. Again, it's so easy to show non-inferiority. I think if we make this a very heterogeneous group with abscesses which may or may not be drained, surgical wounds that may or may not be debrided and diabetic feet which may or may not have osteo-myolitis and polymicrobial infections, you're going to end up with this tremendously heterogeneous group and everything will look the same.

BARTH RELLER: Dr. Leggett.

JAMES LEGGETT: I would also throw out anybody whose had any amputation for ischemia, because if their stump gets a wound infection it's not like anybody else we're talking about here. So I mean I think it's not -- we can't just limit it to diabetes. I think if you're trying to limit it to acute staph and strep infections, that's one thing.

And then my point was just to say just because you're diabetic doesn't mean you can't have a staph and strep infection that's like everything else. But I would also, if we're talking about who to throw out, anybody who's had a BKA (ph) before ischemia is not going to be like anybody else we're

 

talking about if they have a wound infection.

BARTH RELLER: Dr. Weidermann.

BERNHARD WEIDERMANN: Being a pediatrician I'm probably one of the two people, two members up here who doesn't deal with diabetic foot infections and doesn't know a thing about them. But another analogy is spinal injury or spina bifida patients with foot infections. And again it's not the same vascular component, but neurological component, it's polymicrobial, it has the same chronicity dealing with diagnosis of osteo-myolitis. And I wonder if that's another separate entity as well.

BARTH RELLER: Dr. Cox. Do you want a vote on this? Because I think there's, to me at least, there's a consensus that may require more effect on the precise definitions for protocol development. But that there are patients with diabetes with sufficient ischemic vascular impairment and neuropathy, particularly associated with persisting plantar ulcers, that may -- and are frequently complicated with osteo-myolitis, that those patients should be delineated as to where would be excluded, but that diabetes in and of its, of the different varieties and levels of glucose tolerance and hemoglobin A-1s, etcetera, that that in and of itself is not an exclusion with

 

acute cellulitis or acute other problems in this category, post-operative wound infections, for example.

There are a lot of diabetes with wound infections that we haven't discussed. So I think it would seem to me to be a mistake to categorize all patients with diabetes the same, but that there is an entity where other factors are so crucial to outcome that it would be -- it would dilute the precision with which one could evaluate antimicrobial effect in the other larger group of patients.

ED COX: Dr. Reller, yes I think this discussion has been very helpful. I don't think we need a vote on this one.

BARTH RELLER: Question number three. Of course, Dr. Septimus.

EDWARD SEPTIMUS: I'm sorry, I just want to follow up on Dr. Rex sort of got in the cobwebs of my brain, but not all diabetic foot infections are the same. And in fact, as I recall the fetted foot article from the Reviews of Infectious Diseases, I think it was 1979, in fact categorized them into A, B and C. And (inaudible) acute, most of them were staphylococcal and some of them were strep. And one of the things that distinguished that from C, which was the polymicrobial, the one that needed multiple operations and

 

debridement which I think we all agree should be excluded, was that they had -- that they didn't have neuropathy and other things.

So I think there is a subgroup of diabetics that would fit into the acute soft tissue infections that would be acceptable. And I'm sorry I didn't -- I remember where I -- is that correct, fetted foot, 1979?

[off microphone conversation]

BARTH RELLER: The year is impressive enough. Question three. "Given that the data evaluated for determining treatment effect in skin infections included data from various types of skin infections are non-inferiority trials acceptable for the indication of uncomplicated SSSI? Some discussion and then the vote. Dr. Kauffman.

CAROL KAUFFMAN: Could I ask a question of the pediatricians. My sense is impetigo is a risk factor for GN, post-streptococcal GN. And I assume you treat all of them, or am I off base and do you not treat some of them?

KATHLEEN GUTIERREZ: Okay, the question is about impetigo. We treat some of them and we treat almost all of them in various ways. I mean it depends. Sometimes they're treated topically, sometimes with oral antibiotics. It's -- you know,

 

I'm sort of grapping with uncomplicated -- I mean I think of impetigo as being the least complicated, I guess of all of the staph and skin infections and then everything after that is incrementally worse.

But in general the answer to your question is we do tend to treat it. And I don't know if Bud wants to comment.

BERNHARD WEIDERMANN; Yeah, well I'll just say that there aren't good perspective randomized study but there's pretty impressive retrospective data that treatment of skin infections doesn't prevent post-streptococcal glomerulonephritis so that would not be a reason to treat.

You don't gain any prevention like you would for rheumatic fever of streptococcal pharyngitis.

BARTH RELLER: Thank you, Dr. Weidermann. Dr. Alston.

KEMPER ALSTON: Just from a trialist's standpoint, I wonder in this day and age, with the changes in healthcare, whether the patients that have been described today with uncomplicated infections are actually going to be admitted and are going to actually be under our eyes and available for conduct of these trials.

BARTH RELLER: Dr. Fleming.

 

THOMAS FLEMING: We've had a lot of difficulties in defining complicated and uncomplicated. As we try to define uncomplicated there are a number of categories that we've talked about. Minor skin abscesses, folliculitis, furuncles and I think I've pretty consistently heard that surely we couldn't include those categories and do a non-inferiority.

Impetigo is a setting where we actually can do randomized, placebo controlled trials. The Ultabox (ph) trial was just finished. And there are several, many ongoing randomized, placebo controlled trials in this setting. Everything is benefit to risk. The lower the level of benefit the greater the concern that risk could be at a more moderate level and trump benefit. And so understanding level of efficacy very clearly is very important, also as you have lower levels of efficacy.

And understanding efficacy in a setting like this would clearly be more straightforward in a superiority trial. A superiority trial also allows more inclusiveness in who you allow in. If you did a non-inferiority trial right now I could think of at most being able to include impetigo, and I'd struggle with justifying that non-inferiority margin on the posity of data that we have for what the actual benefit is.

 

Maybe uncomplicated cellulitis could be in there too, but we haven't even defined it clearly yet and we don't have the data upon which to base non-inferiority margins. So it would be premature to include them.

So actually it would be a whole lot easier to assess efficacy with a placebo controlled superiority trial than in this setting with non-inferiority. And then Dr. Alston's comments are right on target when it comes to the issue of interpreting non-inferiority. He's exactly right about the fact that any trial needs high quality conduct, but a trial that is done with non-inferiority requires a higher level of assurance of high levels of quality conduct, to be able to understand.

Beacuse he's right, when there's noise in a trial that leads to lesser detection of a difference, in superiority (inaudible). If there's noise towards no difference you might be underestimating benefit. And if you see benefit then you can be confident. But in non-inferiority, if there's noise and it leads to making things look the same, then that could lead you to concluding things are the same when they're really not.

So if I were a sponsor in this area, the concept of trying to do this with non-inferiority, having essentially impetigo as my basis, struggling really to justify a margin and

 

then having to deal with all of the aspects of higher levels of quality of study conduct, it would be infinitely more straightforward to be doing a far more interpretable placebo controlled trial where there is equipose (ph) because of all the things -- when we heard earlier from Dr. Thomas about issues of injection site pain or the associated down side that would occur, the unintended off target effects, those are fully acceptable in pneumonia when you are preventing death. They're fully acceptable if you're preventing a major morbidity. Impetigo's not a major morbidity.

And so to truly understand benefit to risk in this setting and to make the study much easier to conduct, why wouldn't you do it as a superiority trial?

CAROL KAUFFMAN: Could I ask one more --

BARTH RELLER: Dr. Rex and Dr. Kauffman.

JOHN REX: I actually have a question to the pediatricians about impetigo and placebo controlled studies. There's actually, at this point, I think a reasonable amount of data that says that therapy of impetigo, if only topically, actually does have a pretty good size treatment effect. I mean it's actually more than is -- I should say that when you start digging around the literature, you know, you found some other

 

papers, Brad found some other papers, there are actually a lot of papers out there that we didn't all find. Actually I had (inaudible) do a search as well.

And between the literature search that we did, the literature search the FDA did and the literature search that Brad Spellberg did, there were 231 papers, or 230 odd papers. Some of them are things like guidelines but about 200 that were sort of clinically relevant. There's actually only one that everybody found and there were about 20 that two of the three groups found. So there are lots of papers out there that we haven't really used yet.

But for impetigo, our summary of it suggests that there's a pretty good size effect. And my question is post altabacks (ph) post (inaudible) where we've got these reasonably good size effects, are you comfortable in the current era, with recommending another placebo controlled study? And I'm actually cognizant of the fact that there is a downside to a kid having impetigo. And that is that school sends him home and mom can't go to work. So I mean there's actually a limitation there as well.

So what would be, to the extent you think you can represent it, do you think it's okay in 2009 to do that as

 

opposed to several years ago? Where are we with impetigo?

BARTH RELLER: Dr. Gutierrez.

KATHLEEN GUTIERREZ: Okay, well I think one of the things that's changed slightly with impetigo recently is the issue of MRSA. And you know, so that may be a factor to consider in this. Looking at, you know, in thinking about the altaback study, I mean if you look at the group that got -- I don't have the numbers with me, but if you look at the group that got the placebo, there were no bad, long term side effects. And so that's why I'm thinking that if you could show superiority of an antibiotic that was safe, that was probably oral, that had a good benefit/risk ratio, then I think a superiority study would be useful in those children. And that's what, you know, my impression of that is.

BARTH RELLER: Dr. Kauffman.

CAROL KAUFFMAN: I just had another question and that is are there any public health aspects of this, should we not treat impetigo and just let it go from kid to kid in the school setting? Or is that not a major problem or in the family?

KATHLEEN GUTIERREZ: Dr. Weidermann, do you want to take that question?

BARTH RELLER: So Dr. Weidermann --

 

BERNHARD WEIDERMANN: Gee, thanks.

KATHLEEN GUTIERREZ: We'll go back and forth here.

BARTH RELLER: Is there evidence that antibiotic intervention truncates spread?

BERNHARD WEIDERMANN: Short answer, no. That's the -- you know, we'd love to have more data on that and I guess some is on the way or being assembled anyway, larger studies. You know, and in answer to Dr. Rex, I think still the magnitude of the benefit of treatment is low enough that maybe I wouldn't get ethically concerned about a placebo controlled trial. But if I put myself in the investigator role in trying to explain this to a family, you know, I can explain it with a good conscience, but I don't think I'm going to get a lot of takers.

JOHN REX: You know, I think it is it's ethics, it's not not pragmatics. That's the challenge.

BARTH RELLER: Dr. Fleming and then Mr. Davis.

THOMAS FLEMMING: Everything is benefit to risk, as we've said repeatedly. But it's not a novel situation to say, even in settings where you have shown much more clearly than we have, that an intervention is effective, much more clearly than we've shown antibiotics truly provide benefit in impetigo. There are settings of pain relief, analgesic studies, there are

 

anti-asthmatic studies, there are anti-psychotic trials where you have interventions that have shown effect nevertheless with informed consent it's still very ethical to randomize patients to an experimental therapy against a placebo, because the nature and the level of the effect isn't that profound.

Plus, every intervention has risk. Even antibiotics have risk. And it isn't so obvious that minor benefit exceeds the risk. And so benefit to risk has to be factored in. It's -- and there's ample precedent to indicate that when you have an intervention that is not a major morbidity/mortality outcome that you're going to find, ethically, the most reliable evidence about whether this is an intervention that should be used when the overall level of effect is so limited and controversial that randomizing to a proper control and looking at superiority allows you to strengthen your sense of what that benefit is and to put it into context of what the risk is for judging whether it's favorable benefit to risk.

And again, there are -- it's not just that we have recently finished the altabox trial, there are other studies including a number of ongoing studies that are now underway that are looking at randomization against a placebo control in uncomplicated disease. These are recognizing that in this

 

setting the level of benefit, while potentially important here, needs to be established in order to justify that it exceeds the ongoing risk that is apparent for any intervention.

BARTH RELLER: We'll next hear from Arthur Levin the consume representative on the committee.

ARTHUR LEVIN: I would just second -- I mean Tom said what I was going to say that it seemed to me this was the kinds of issues people are concerned about are the issues that people raise with all placebo controlled trials. The level of discomfort of subjects in possibly getting a placebo, the level of discomfort in the investigator in giving people placebo. So that's always present. But again within informed consent process and people volunteering in an informed way to go into these trials, it doesn't seem to me to be an ethical issue.

BARTH RELLER: Dr. Rex.

JOHN REX: Tom, I thought about the schizophrenia case as a parallel and there is a difference between that and impetigo which is the case of offering a schizophrenic a placebo for a period of time. The only person who is involved in that is that human being, you know, that person's the one not getting therapy for schizophrenia. Whereas, with impetigo I guess -- I am not a pediatrician, but I can imagine being on the other end

 

of it, I'm thinking about the other family members, I'm thinking about the kid not being able to go to school and I'm thinking about MRSA spreading.

And so I'm just wondering about that. But it really would be easier to do the superiority study because that's clear, it's probably a smaller study. There are lots of advantages to it.

I guess my wish would be that guidance in this area retains some flexibility because you might go from a point where you felt like you were comfortable doing superiority studies to one where you thought well, I've kind of crossed the bridge on this and, you know, it's now clear that MRSA 5000 that's now circulating is bad news if you don't treat it, and so we've moved on to where we can't -- we can no longer do placebo control even for this setting.

I mean you know, you can imagine that occurring. So I would encourage guidance to anticipate the possibility that you might find in the future that you would -- that for some reason you need to do non-inferiority. And, you know, there is an increasing body of data to support the idea that there is a treatment effect. It's probably enough to get you a margin.

BARTH RELLER: I think it's time for a vote. Oh --

 

KATHLEEN GUTIERREZ: Actually can I just respond?

BARTH RELLER: -- and then the vote.

KATHLEEN GUTIERREZ: I'm just thinking of the transmission issue. I mean the reason that we treat impetigo in children is, you know, the primary reason is not to prevent transmission of organisms, you know, through the school, it's mostly to treat the child itself. And so we do talk about issues in terms of good hygiene and that sort of thing. And, you know, even if you're treating -- I mean if you're treating a MRSA infection one of the things that's most crucial is the issue of good hygiene. And it's not so much, you know, that we think that treatment is going to eradicate colonization, for example.

So I mean I think we would have to figure out a way to quantitate what that would be, you know, that effect of preventing transmission.

BARTH RELLER: Dr. Septimus wants clarification before voting.

EDWARD SEPTIMUS: Just a point of clarification. We've been talking a lot about impetigo but I -- unless I misunderstood the question, that's just one of several uncomplicated SSIs that we're talking about We're not voting

 

specifically on just impetigo, I just -- is that correct?

BARTH RELLER: It is a major component of uncomplicated, but you're correct. It's uncomplicated as a category of SSIs.

EDWARDS SEPTIMUS: And a lot of the small abscesses we talked about previously probably would fit under this category as well, I'm assuming.

BARTH RELLER: Correct. Dr. Fleming.

THOMAS FLEMING: Just on this point, because you're right. And the agency had already qualified, in their discussion before, minor skin abscesses, folliculitis, furuncles, these wouldn't be in a setting where you would do a non-inferiority, you could do superiority. We focused on impetigo because that's the one setting in which there is some evidence here, there other settings too, uncomplicated cellulitis, and we're sitting here trying to find out what the definition is, much less having data to defend a margin. So I think that's why the focus of the discussion got into impetigo, because you need data.

And just one -- if you're going to look at other people, and we've already refuted this issue of spread, then okay then a counter-balancing argument is if you're using

 

antibiotics in a setting where it's not really well established you have favorable benefit to risk, you're enhancing development of resistance. That's going to affect other people negatively.

BARTH RELLER: Thank you. Three options, yes, no, abstain, 20 seconds please. We have an overwhelming proportion of the committee that things that non-inferiority trials are not ideal for uncomplicated skin and soft tissue infections. At this time we'll go left to right for any additional comments that one wishes to make with this decisive vote for what trials would be appropriate. Dr. Katona.

PETER KATONA: Well I think any time you can justify a placebo controlled trial, a superiority trial, over a non-inferiority trial I think you should go for it. And I think this is the case here. You know, antibiotics have risks, you have to take that into account, you can probably get this through human subjects committees a lot more easily. And so voted no.

BARTH RELLER: Thank you, Dr. Katona voted no. The overall voting was 16 no's for the record, four yes's. So when one introduces the comments, particularly the four who voted yes, to way why you voted yes, but also the 16 who voted no, as to why you voted no and what your alternative strategy should be

-- or would be recommended. Dr. Alston.

KEMPER ALSTON: I voted no. I agree that if there's any change of doing a superiority trial you should because the non-inferiority design is so flawed, as we've come to understand.

BARTH RELLER: Dr. Goetz.

MATTHEW GOETZ: I'm actually chagrined because I pressed the wrong button. (inaudible) stop and almost start right there. I believe that there are important challenges in doing a superiority study in terms of defining what is an uncomplicated skin and soft tissue infection. The issues of where that dividing line in cellulitis is will be particularly challenging. I recognize that protocol development enrollment will be complicated for reasons that we previously discussed. But on the whole, given the severity of the infections, the list of complicates that may ensue if a person's not immediately treated and given the data which are available at present, a superiority trial, I believe is the right strategy.

BARTH RELLER: Dr. Fleming.

THOMAS FLEMING: I agree with my colleagues. You are in a far more interpretable mode to be doing a superiority trial. Patients join trials not just for their own benefit but

 

for altruistic purposes as well. And those altruistic purposes involve trying to find reliable insights about the questions that need to be answered. And the far and away most reliable insight you're going to get here is from a proper controlled superiority trial that allows you to understand whether there is a magnitude of benefit that truly does over weigh or outweigh the risk that is apparent with any intervention.

And the quality of study conduct issues are much more easily addressed in a superiority trial. And the inclusiveness of the enrollment is much broader if you're going to do a superiority trial. So the superiority trial has many specific benefits. In terms of the end point in a superiority trial it would be resolution of symptoms or time to resolution of symptoms, clearing of crust or lesions from impetigo, clearing of redness, swelling, warmth, tenderness, etcetera. It would be looking at getting more timely resolution or a more substantial fraction that have resolution by some point in time.

BARTH RELLER: Dr. Leggett.

JAMES LEGGETT: I voted no on the basis -- on what's already been said, but also really on limited data on which to base a non-inferiority trial, a limited definition, expect for impetigo, of what we're talking about. And then with all those

 

limitations I can't understand why any company would bother applying for this unless they were a company with a topical antibiotic.

BARTH RELLER: Dr. Bennett.

JOHN BENNETT: I guess I was lulled into a disinterest by an increasingly repetitive discussion about trial that no company would be interested in doing, so I punched the wrong button.

BARTH RELLER: Dr. Lesar.

TIMOTHY LESAR: I voted no. And again echo the comments about limited data as well as difficulty assessing risk and benefits.

BARTH RELLER: Dr. Nelson.

LEWIS NELSON: Yeah, I voted no as well, for the most part it relates to the relatively low risk of the infection and the relationship of the risk/benefit ratio to that.

BARTH RELLER: Dr. Septimus.

EDWARD SEPTIMUS: I voted no for all of the reasons already stated.

BARTH RELLER: Miss Thomas.

JEANINE THOMAS: I too am guilty of pushing the wrong button. But -- and from anybody has stated too, I think

 

superiority trials are just the way to go with this. And sorry about that.

BARTH RELLER: Dr. Steckelberg.

JAMES STECKELBERG: No. Further would be redundant.

BARTH RELLER: Dr. Cross.

ALAN CROSS: I also voted no for all the reasons mentioned. But I would also be interested in the efficacy if a superiority study were done on just the hygiene issues that Dr. Gutierrez mentioned. How good is the hand washing and other issues (inaudible).

JOAN HILTON: Well I voted yes and I guess I'm the only one standing by my yes vote. And I was moved by a comment by someone on this side of the table who said why don't we leave that option open. Why don't we just allow non-inferiority trials even if we might prefer superiority trials. So just building on that thought.

There's also kind of a hybrid between these two where often non-inferiority alternative hypotheses seek equality and a possibility is to seek superiority as the alternative. So I just am trying to be more flexible in this setting.

BARTH RELLER: Mr. Levin.

 

ARTHUR LEVIN: I voted no for all the reasons stated. And maybe we need to investigate these voting machines, I'm not sure given the amount of false negatives.

BARTH RELLER: While this question is fresh, I did the same thing as two other members of the wrong button, but I had the advantage of right hand Dr. Kim telling me what to do. You can press the button as often as you want to, you're not going to get any reward for doing it, but you can press it. And it's the last touch that counts for tomorrow and the next day. Dr. Weinstein.

MELVIN WEINSTEIN: I voted no for the same reasons as the others.

BARTH RELLER: Dr. Follmann.

DEAN FOLLMANN: I voted no for pretty much the same reasons. The only thing I might add is you know, instead of a pure placebo controlled trial you could consider a delayed start trial where you randomize to the immediate drug, or placebo followed by drug for everyone after a period of time. And your end point for that would probably be time to cure rather than cure at a specific time. So you'd have to measure whether there'd been cure repeatedly throughout the study. But that might be a superior trial design. It could be used sometimes

 

where pure placebo couldn't.

BARTH RELLER: So you would -- it would be improvement resolution of symptoms after initiation of therapy, be it immediate or delayed?

DEAN FOLLMANN: Well I would probably just look at time to cure basically, thinking that if you delay treatment by seven days probably, you know, their cure times would be seven days later than the other. And so, you know, you could work it out and it should be a fine design.

BARTH RELLER: Dr. Gutierrez.

KATHLEEN GUTIERREZ: Well I voted no for some of the reasons I stated previously. But in thinking about this it's going to be a little complicated because I think impetigo is different than superficial skin abscesses. And I, you know, trying to figure out a way to -- I guess the next discussion would be whether we have to separate or lump those. Because, you know, with superficial abscesses you can incise and drain and impetigo you can use topical treatment. So I think there are some differences within that group already.

BARTH RELLER: Dr. Kauffman.

CAROL KAUFFMAN: I voted no after hearing from the pediatricians that impetigo wasn't as worrisome as I thought it

 

was. I'm worried that in fact it'd be hard to enroll into that study because a lot of parents are going to want something and they'll go to the next doctor and get (inaudible) if you try and put them in a study. But that's neither here nor there right now.

BARTH RELLER: Dr. Weidermann.

BERNHARD WEIDERMANN: Well, I voted no but, and just to add something different here, I think -- you know, I voted no because I can't think of a situation where a non-inferiority trial, you know, would have the justification for it. But it may be in something like what Dr. Fleming was talking about, a mild cellulitis, whatever that is, if we could get information. I've certainly treated mild cellulitis, however I've defined it with oral antibiotics as an outpatient. And maybe whether combining that with Dr. Follmann's idea of delaying start of therapy, maybe there's something in there. But we just don't have the data right now to know how to go about that.

BARTH RELLER: I voted no. The reasons have been articulated. But just one point of emphasis. I was persuaded by the epidemiological considerations and emergence of resistance. And where there is a small treatment effect these other components become much more important. And as Dr.

 

Weidermann pointed out, with informed consent and honest exposition, I think, at least I would hope over time that there's greater public recognition of the importance of antimicrobial resistance. And if we honestly do not know whether these antibiotics make a difference, it would be legitimate to show it. So that when an antibiotic subsequently be used, if it's shown to be superior, it would be with recognition that that utility overrides the downside.

Question number four, we have in our allotted time about 25 minutes and given the complexity of the discussions, the extent of the discussions that are taking place, I think it is entirely doable to give at least balance or fair consideration to this question in the 25 remaining minutes.

"Should uncomplicated studies only enroll patients with infection such as impetigo, erysipelas and cellulitis and exclude those with abscesses?"

This question is more complicated than what meets the eye, I think, given our earlier discussions. But it is now open for discussion.

MATTHEW GOETZ: I'm somewhat troubled by the conclusion of erysipelas as we've defined and discussed that earlier this morning with a 10 percent mortality rate. Is that

 

what the FDA intended or am I misinterpreting the language here.

EDWARD COX: You know, I think we're talking about milder manifestations. And I guess the question with some of the discussions that we've had here today, would be -- maybe the way to address the question would be what types of infections would you include in an uncomplicated skin and skin structure infection.

BARTH RELLER: Because I think that you're absolutely right and that's why it's more complicated than meets the eye. I think there is a consensus, in fact the last vote with corrections for electronics was actually 19 to 1. And the previous one 20 to 1 for utility under defined circumstances versus better alternatives.

So that the key is in the definitions. And what one would be talking about here with uncomplicated is the kinds of infections that would be legitimately included in a superiority trial.

So is that all right to rephrase it? I mean after discussions along those contours?

EDWARD COX: Yeah, that sounds good.

BARTH RELLER: So what are the committee's views on what kinds of infections that have been discussed today would be

 

legitimate targets of superiority trials or the obverse of that, would with the limitations discussed, not be best studies given some flexibility that Dr. Hilton referred to by a non-inferiority design? So comments? Dr. Fleming.

DR. FLEMING: And still maybe just a clarification or a context. I think in view of question three it would be -- I would focus on the answer of question four in the context of doing a superiority trial which allows, in my view, more flexibility in who you would allow into the trial, because you're not needing to restrict to those sub elements where you have already established a non-inferiority margin.

So while we had clearly left out minor skin abscesses, folliculitis, furuncles and because we don't have any data on margins on complicated cellulitis, those can all now be on the table for potential consideration in superiority along with obviously the impetigo. So I would just say it -- there is to me a wider spectrum of potential cases that you could allow, under the understanding that they're all meeting the definition of uncomplicated, where it would be appropriate to be doing a superiority trial.

So having said that, the question would be how broad a setting is it likely that your intervention would have

 