sensitivity or would have a meaningful effect? And if it would have a meaningful effect in a broader setting of uncomplicated situations, then I would argue to allow those patients into the trial. So it's really a question for my clinical colleagues, once we focus on uncomplicated, where we have accepted it would be appropriate to do a superiority trial, is it reasonable to anticipate that you would have likely important or comparable level of benefit in minor skin abscesses, folliculitis, furuncles, impetigo and some definition of uncomplicated cellulitis? Or are there subsets of those that you think would far and away be more sensitive to benefit?

BARTH RELLER: Dr. Kauffman?

CAROL KAUFFMAN: I would say that the only two things that I'd be interested in giving antibiotics to would be impetigo and small abscesses. But folliculitis and furunculosis generally just aren't treated and I can't imagine putting them in a study. And cellulitis, cellulitis to me needs to be treated and I consider it complicated.

BARTH RELLER: Dr. Rex.

JOHN REX: I just want to be sure that I had straight in my head that the committee was lined up on what it meant to be over the edge, in terms of it's got to have

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antibiotics. And we did talk earlier, and so I'm first talking about the definition of what's -- I guess there's truly uncomplicated, and let's take impetigo as sort of the prototypical truly uncomplicated. Somewhere over to the right there are -- there's real erysipelas, real cellulitis. And somewhere in between those things there's got to be a tiny version of erysipelas, a tiny version of cellulitis.

I'm sort of struggling to describe this. And the idea that I thought I heard was that the distinction begins -- if you truly believe that you've got a tissue infiltrating process with a bacterium, even you know a patch of cellulitis, a patch of erysipelas, the only time that that's uncomplicated, if this is what I heard and that's what I want to ask, is when it's a normal host who has no symptoms with it. So that would be the requirement, and maybe it's not a scary -- it's not in a bad place. So if you sort of meet those criteria that's uncomplicated erysipelas, you know, whatever that is, uncomplicated cellulitis.

But if it's a abnormal host, or there are symptoms or if it's in a bad place, tissue infiltrating process, even if it's not dramatically large right now, that's probably falls into this category of complicated. And that's what I'm asking

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to have verified. I think that's what I have heard the committee say is that you have crossed the boundary at that point and basically that's what Dr. Kauffman said. Is that a fair sense of it?

THOMAS FLEMING: Could we ask FDA to give their definition again? FDA gave a definition at the beginning.

BARTH RELLER: Dr. Cox.

EDWARD COX: I can give you the definition from the '98 guidance -- draft guidance document. It's "The uncomplicated category includes such clinical entities as simple abscesses, impetigenous lesions, furuncles and cellulitis, infections that can be treated by surgical incision alone such as cases of isolated (meaning one solitary area of infection), furunculosis or folliculitis should not be included in clinical trials." So that's for uncomplicated.

For complicated, just to have the contract, "The complicated category includes infections either involving deeper soft tissue or requiring significant surgical intervention such as infected ulcers, burns and major abscesses or a significant underlying disease state that complicates the response to treatment. Superficial infections or abscesses in an anatomical site such as the rectal area where the risk of anaerobic or

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gram-negative pathogen involvement is higher should be considered complicated infections."

BARTH RELLER: Dr. Rex.

JOHN REX: And it was that line about "and a significant underlying disease state that complicates response to treatment" that drives me to talk about abnormal hosts or bad locations. You know, that's what I'm cueing off of. And when you look at recent trials, people interpret those somewhat differently but, you know, the themes are as I have outlined.

THOMAS FLEMING: Although I didn't hear symptoms, so you had actually said symptoms would put you into automatically complicated, I'm not hearing that.

EDWARD COX: And Dr. Fleming you are correct, however looking at protocols and the inclusion/exclusion criteria, symptoms would also typically be you know, part of a complicated definition. You know, there'd be a listing of a number of different clinical findings and, you know, various symptoms, you know, fever, you know, white count, those types of things would the types of additional findings that would push you into a complicated category.

BARTH RELLER: Dr. Goetz.

MATTHEW GOETZ: I think though as we started to talk

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about what could be uncomplicated cellulitis, we have to recognize that our diagnostic tools for cellulitis that involves no constitutional symptoms in a physiological normal host, in a a non-jeopardy location, our tools are very poor for making that diagnosis, because what we're going to be basically left with is red skin.

And our specificity for knowing that's due to bacterial infection rather than another cause is so poor. When we're certain, and we have diagnostic certainty that it's cellulitis, it's almost always complicated and requires antibiotic therapy and it'd be very difficult to enroll patients in such a study where they might be randomized to get no therapy.

BARTH RELLER: In following up on Dr. Cox's definition it would seem to me, from the sense of today's discussion, that there entities that clinicians feel are caused by bacteria that may response to therapy, but that from these discussions that the appropriate place to -- or the method of studying them would be a superiority trial where you wanted to show effectiveness but where currently these clinical entities -- it's not sufficiently certain that there is a therapeutic effect over and above placebo or simply drainage. And those are

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the ones.

I mean if they were not infected at all, I mean there was no organism, then how could you show a difference, and why would you waste money doing a clinical trial? So there has to be infection, antibiotics may make a difference but we don't know how much of a difference and those are the ones that you want to enroll in this trial.

And if it's necessarily to give antibiotic therapy to preserve life or function, they're not candidates for such a superiority trial, and they are not uncomplicated. Now I realize that one has to be more precise than that but that seems to me the sense of what we're going after here. Other comments? Rex and Fleming.

JOHN REX: The 1998 guidance was -- I mean Tom asked Ed to read that into the record, those guidances were not extensive -- this has been sort of deepest debate I'm aware of in the public forum about them. And I think it's been helpful to me to hear that debate. And point at the old literature and sort of put it all in context that the people in the old literature who went to see a physician were ones who came because of symptoms.

And so that is -- I think that's got to be the path

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to physiologic link is that if there's some constitutional response to it, that's probably the thing that gets you over the border and those are folks who probably need a drug rather than just observation, because that suggests that there's something going on. And so it's the -- so the break that I keep hearing is normal host, asymptomatic and but beyond that that's where if it's an abnormal host or they are symptomatic, they've come for a reason and that's the group that does have at least some portion of the effect that we heard about this morning.

It may seem I'm picking very finely on this point but I am interested in being sure that we recognize that there is a mild version at presentation of what could -- of complicated -- complicated is such a bad word because we conflate the severity of illness with the severity of the (inaudible) with the risk for progression all in one term. And that's what's kind of driving us nuts right here.

But I do want to recognize there's a milder version at presentation of a syndrome that is the beginning of complicated skin infection and that those folks are the ones who would progress and those folks do have a treatment effect. And that's the point I think that the committee seems to be dancing around the edge of. And I'd like to just lay it out on the

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table and say it.

BARTH RELLER: Without getting into a specific temperature or white count or shift to less mature forms it would seem that what we're really talking about is where there is -- when there is absence of systemic or hematologic response in a patient who has the capacity to respond. And it seems to me one could come up with some boundaries there that would be reasonable to include patients who did not have those aspects. Dr. Steckelberg.

JAMES STECKELBERG: Just a question. This may have come up in discussion before but where do the superficial surgical site infections, the superficial ones that respond just to opening the wound, where did those fit in?

EDWARD COX: Do you want me to try, Dr. Reller?

BARTH RELLER: Well I was going to say it depends on whether they have those -- you know, the elevated white count, etcetera whether the cellulitis is spreading out or whether taking out the stitch it all resolves quickly.

JAMES STECKELBERG: well I assume if they're toxic or they have septic symptoms, then they're complicated.

BARTH RELLER: Dr. Cox.

EDWARD COX: No, that's fair. I mean it's a

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question of what actually is going on with that wound. I mean given that it is a wound, it would, you know, it would be something that would typically be in the complicated category but you know, the question of what's going on with that wound, is there surrounding cellulitis, is there something, you know, that needs to be done beyond just simply opening up the wound.

JAMES STECKELBERG: So then I assume some of them would be uncomplicated and should they be included then. Your question is what should be included to enroll patients there, would that also be a category?

BARTH RELLER: Dr. Cox.

EDWARD COX: I guess I mean I think you're bringing up an important point, and that is, you know, thinking about, you know who are these patients and what do we know about you know, the likely effect of antimicrobial therapy in them. You know, in the setting where, you know, and this has I think been brought up, you know, in the discussion so far, in the setting where we think there really is something that may progress there or that there may be problems, and you know, perhaps maybe that group of patients with wound infection would be appropriate for complicated skin. Whereas, if simply opening up the wound is going to be enough to make the infection essentially resolve,

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then perhaps that would be something that would be appropriate for superiority design. You know, where in fact the benefit of antimicrobial therapy would be less clear.

But I think you're bringing up -- you know, also the important point that this is something that we'll need to be mindful of when we talk about you know, wound infections.

BARTH RELLER: Dr. Kauffman.

CAROL KAUFFMAN: Could I just make a comment that I think erysipelas just doesn't belong in here. I mean the classic definition of erysipelas is a systemic illness. It has a border, it's clearly spreading, those patients are really ill. And so I think it's the wrong word in the wrong place. John, there may be mild cellulitis, but I'm not sure there's ever mild erysipelas.

JOHN REX: But I think that's what Brad said as well. I'm just -- I was trying to get out the definitions and be sure that we'd beaten on it because we've gone to a lot of trouble to get to everybody in this room to have the conversation and I would hate to miss the opportunity to discuss it.

BARTH RELLER: Dr. Fleming.

TOM FLEMING: I think Dr. Kauffman's response way

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back at the beginning is still largely in place having gone through this discussion that either folliculitis and furuncles would be uncomplicated, it's not probably where we would go, we would go towards minor skin abscesses and impetigo. And whether we would get into cellulitis has been again cast in doubt because we're struggling with defining what an uncomplicated cellulitis is.

There are four ongoing major trials, two of which are being done by NIAID and I was just looking at one of these. It's a stratified, randomized placebo controlled trial of bacterium for outpatient treatment of cellulitis, including erysipelas and/or abscess in children and adults. So it'd be really interesting to get into that protocol because they do seem to be pushing at least into being a little more inclusive than we just said.

But certainly what Dr. Kauffman indicated seems to be well within the range of what you would consider an appropriate superiority trial setting.

BARTH RELLER: Other comments? I do not think we need a specific vote on this question. Dr. Laessig and Dr. Cox, any additional queries for the committee?

EDWARD COX: No I think the discussions have been

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very helpful. You know, I think there's a number of challenging issues that we've been able to discuss this afternoon. And we appreciate everybody's thoughts and comments.

BARTH RELLER: I should like to thank all of the committee members for their rigorous discussion and contributions. We will reconvene at eight o'clock tomorrow morning. We've discussed margins and I'm happy to say, thanks to your splendid cooperation, we're less than a margin of one percent of the total of time allotted at four minutes to five o'clock. Thank you very much.

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