argue it wouldn't is I can't sort out from those papers which ones would match and which ones wouldn't match.

DR. TEMPLE: Yes, well doing it is another matter but that is the intuitive feeling I am hearing from people. A lot of these people who would have been in --

DR. MUSHER: That is --

DR. TEMPLE: -- before.

DR. MUSHER: -- the truth.

DR. TEMPLE: Okay.

DR. VENITZ: I just wanted to agree with that. That allows me then to translate not only the mortality results that we find in those old studies to translate them into failure rates, clinical failure rates, because you are looking at a different endpoint. But I still think that the patient population is different.

DR. TEMPLE: And I take it a high likelihood that it is bacterial would be important here also --

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DR. VENITZ: Absolutely.

DR. TEMPLE: -- to make you convinced that they would do badly?

DR. MUSHER: Absolutely. And again, one of those backup slides that I showed was from the Heffron textbook showing that in the 1930's, 96 percent of everything that they could call pneumonia was attributable to pneumococcus.

ACTING CHAIR TOWNSEND: Dr. Rex?

DR. REX: Dr. Temple has commented on the importance of trial quality and getting microbiology. And I said it was important earlier in the sicker folks. It is even probably more important here that we have a good microbiological -- sorry, we have a good clinical footprint supported by a pretty significant amount of microbiology. And that should be achievable.

This severe business, mild business, sometimes I think it helps to actually get a picture in your head. And let

me, I am just going to pick one.

Case 6142. Man age 44 admitted as a control case, which means he is not going to get treated, about the third day of his illness with bilateral lobar pneumonia, pneumococcus type one. Three doses of polyvalent antiserum were given daily from the day of admission.

So, think about him initially. He doesn't sound too sick. They are not saying he is dead yet. And then they say -- but he sounds pretty sick. But would he have been an outpatient today? It kind of sounds like he might have been because it isn't until the third day that he started to get worse and now delirium is well marked by the third day.

So, when you think about this guy, he was probably not, he was kind of on the edge three days ago. And then over a period of three days he actually deteriorates. So, I bet this is somebody that you might well have treated orally and yet now in the face of

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no meaningful therapy, he has gone downhill.

So, it is this issue of progressive risk. And this guy is 44, so that puts him kind of beginning in the more severe -- and this guy goes on to die, by the way.

So, it is progressive risk. It is not at the moment. And we do have lots of care systems. We are currently motivated very much to send people home with good monitoring. Come back and see me in the office tomorrow morning. I have got an ER follow-up clinic every day from 8:00 to 10:00, come back in the morning. So, we do lots of things to send people home to spend the night in their bed because that is good for them. It is good for health care costs. And we want to be able to generate some reasonable data. So it is going to be up to us to generate good quality information. And I will remind you. I have said it a thousand times, but I will say it one more time. We are not going to give you just one trial. We are going to give you a

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whole package of data that points to why this dose should have had an effect. And these patients have a good syndrome and at least a fair proportion of them have a microbiology footprint that makes sense.

And we have looked for influenza and we weren't in the middle of an influenza epidemic that we enrolled a whole gob of people with influenza because we looked for that too. So, keep all those things in mind when you think about what it would look like. It is not just an abstract. It is a real thing where we are going to working. The sponsors need to be motivated to chase the good cases.

DR. KAUFFMAN: Could I just make a comment that it is going to be harder in this kind of patient than it is in the person who is in the ICU bed who is captive and you can get all the data you want on them. So, these would be tough studies to do but they are immanently doable, I think and will answer

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important question. And I agree. A lot of people are treated with quinolone. They are sent home. And only later they come back into the hospital when they need to be hospitalized. But early on, most of them stay out and do fine.

ACTING CHAIR TOWNSEND: Thank you. Any other comments on that part of the question? All right, that may have been the easy one. Now comes the tough stuff.

"To which patient population would this information apply with regards to disease severity and microbiological etiologies?" How do we decide which are mild to moderate patients that we treat as an outpatient on an oral agent? Dr. Dowell?

DR. DOWELL: I guess, technically, if I said no, I am not supposed to answer these but I think that people are pointing that way out for those of us who voted no. And that basically is to say, well let's go back and enroll the patients who would have

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been enrolled in the 1940's trial but who could have taken an oral agent. I mean, that is an easy way out because then you can use that for your M1 and then apply these things.

So, to answer number one, you would say you would like this information to apply to those patients who would have been in those trials. So, it is kind of the patient that John is describing.

ACTING CHAIR TOWNSEND: Dr. Musher.

DR. MUSHER: Start by saying that if you are going -- patients who would be included are those who would qualify by the pneumonia outcomes research team, the PORT score would qualify for not being hospitalized and that is a score, as always, modified by clinical judgment. So, if they qualify for hospitalization, we are not going to treat them as outpatients.

I would then say that the question is, do you want to enrich them for bacterial disease or do you want all the viruses and the

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mycoplasma in there too? And that is kind of difficult to say. And I don't know what the answer is.

So, believe it or not, I won't have anything further to say.

ACTING CHAIR TOWNSEND: Dr. Whitney.

DR. WHITNEY: I do think you should try to enhance them for bacterial etiologies. I think that is harder with outpatients because nowadays clinicians don't often get diagnostic tests routinely. So you would have to catch them as part of the trial and get that.

ACTING CHAIR TOWNSEND: Any other comments?

(No response.)

ACTING CHAIR TOWNSEND: Okay, part two. "What endpoints should be utilized in a study of this type?"

DR. MUSHER: I just would say again, as I have said before, I just took a

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look at the idea in the document and it does say fever and the items that are mentioned in that patient report form. And I will propose that it was simply an omission that they didn't mention the severity, the other indicators of severity of disease which refer to things like respiratory rate and pulse.

But that being said, these are patients who have gone home. So, therefore, you really are left with asking them to take their temperature and the patient report forms as discussed.

ACTING CHAIR TOWNSEND: Dr. Venitz?

DR. VENITZ: I think it should be the same endpoints as it was for the inpatients. Clinical success that might involve actually having those patients visited by nurses what have you to do, whatever testing is appropriate.

I do think that the PROs should be evaluated but not being used as primary endpoints. I consider them, at this point,

investigational. And I think somebody said before, maybe in five years the next committee gets together and decides that the PROs are the more relevant. But I think for right now it should be the same clinical success criteria that you use for the inpatient, for the severe patients.

DR. KAUFFMAN: Can I make a comment? I think if you are going to do this trial right, then part of the agreement right up front is the patient visits you in your office very other day or something like that and you take the time to see them and document things from the physician point of view as well. So, I think you would need both ends of that.

DR. MUSHER: Is there an industry perspective on that? Is that a possible thing to do?

ACTING CHAIR TOWNSEND: Dr. Rex, do you have a comment on that?

DR. REX: Well, I always laugh when

somebody says what does industry thing. You know, there is no -- but I tell you what. This corner right here of industry has to say is I appreciate, you know, Dr. Fleming makes a good point. We wish we had a PRO, I truly do because it would be nice. And I was struck by, for example, the oseltamivir versus placebo Nicholson 2000 paper review they recently wrote. It wasn't a validated PRO, but they collect symptoms twice a day on people. And they were able to say, they defined a way the symptoms got better and I thought that was good.

But to say that we are stuck dead in the water until such time as we go through the entire process of validating an official PRO is, I think, a degree of skepticism and angst that is not warranted at present. If you look at the group of symptom -- we have got a sense of it. I showed that slide earlier where what were all the symptoms when people tried to come up with PRO-like things,

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what were the kind of symptoms that they came up with? And you saw the list and it was fever and chills and cough and dyspnea and so forth.

It is hard for me to imagine that a fully validated 100 percent FDA approved psychometrically perfect PRO would differ dramatically from the aggregate, not on any given day, but the aggregate interpretation over an entirety of a patient's course by the average physician. There will be individual mismatches. The aggregate, the physician-based report may not be as precise because it may not be able to tell you how many hours it took but it is overall reasonably accurate. Dr. Musher and I will agree at the end of the whole observation period, Ms. Smith is either better or not. We may differ whether she is failing on day four, day four and a half or day five. But we are not going to differ on aggregate that much.

So, I think that we can work on

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PROs and industry will gladly spend a little time developing them because, who knows, we might come up with a sensitive measure that allows me to say that yes, my drug actually does make people better faster. That is my motivation to do it. I will work on that. But to tell me that I have got to do that in order to do any kind of trials for oral drugs, I think that is a degree of radical skepticism that is not warranted. There is enough match, it is an intuitive thing but it seems very reasonable to me, there is enough match between what would have to be in a PRO and what is already in the clinical response that we have been using. That clinical response can't differ that much from the overall flavor of the PRO. I think that is -- it is hard for me to see anything different than that. Some precision? Yes. But qualitatively, the match is going to have to be pretty good. Otherwise, the PRO is measuring something that I don't even know what it is, if it doesn't

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more or less match the aggregate sense of the patient got better, was ready to eat and was ready to go back to work.

ACTING CHAIR TOWNSEND: Dr. Calhoun.

DR. CALHOUN: So I think that the outcome measure has to be clinical success and clinical failure. These people, by definition, are not going to have physiologic abnormalities that you can measure. One might be able to look at temperature and you could look at time to resolution of temperature as one objective but they won't have abnormal blood gases, by definition. The amount of tachycardia that they have got will be small and probably immeasurably elevated.

So, I think the outcome is going to have to have to be a clinical response with patient reported outcomes. And I would agree with John. I think the notion that these would need to be validated a priori is probably a more rigorous bar than we need

because they wouldn't be a primary outcome, they would be a secondary outcome.

DR. MUSHER: And clearly, has to be a blinded study. Everybody is absolutely in agreement on that.

ACTING CHAIR TOWNSEND: Dr. Temple. The PRO terminology seems to me something of a distraction here. That usually refers to something, you know, with a ten centimeter scale or something like that. I mean, people make clinical evaluations all the time. You ask the patient how sick he is, what his fever is, whether he is coughing a lot. There have always been assessments, I mean, you always do that. And everyone seemed to agree that we are not interested only in death here, we are interested in other aspects of whether the treatment is successful.

So, I think everything we heard made us think you would continue to use that kind of endpoint here, just as you would in the more severe illness. But to aspire to

developing standardized instruments for each of these things or an SF-36 or something like that, I don't think that is what people have in mind. Is it?

I mean, if somebody wanted to show that one drug makes a person feel better in some way and was able to do that with some novel instrument, well that is okay. But you are just trying to find out what the failure rate is because that is what you know. And what we have heard, and I think it is interesting because I don't think we anticipated this, is that you think that a lot of the people who were treated as outpatients are not so different from those really sick people before, but you can't use the same endpoints. And you told us before that that endpoint isn't just death, it is failure of various other kinds to be described. So, aren't you just saying do the same thing here? Or do you really want some kind of special cough instrument? You know, rate your cough

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from zero to ten. Is that what you want?

ACTING CHAIR TOWNSEND: Dr. Rex?

DR. REX: Vigorous agreement.

ACTING CHAIR TOWNSEND: Speaking from a clinician's standpoint, I'm not sure how the other clinicians in the group feel, when I see a patient with pneumonia, I don't have them come back. He is treated as an outpatient. I don't generally have him come back every other day to see how he is doing, or call him up, or ask him to call me if he is not feeling well. I'm not sure if other people have the same approach. That may be sort of a guide to how we deal with this.

DR. MUSHER: And I just want to add that I think that it shouldn't just be a single point at day seven or day 10 or 14. I do think the rate with which the improvement takes place is useful and should be analyzed.

ACTING CHAIR TOWNSEND: Dr. Patterson and then Dr. Fleming.

DR. PATTERSON: Well, I was just

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going to say that yes, we do look at the same clinical morbidity endpoints but it is just that these people are outpatients now, whereas they were inpatients before. And so, just from a practical standpoint, that is a little harder to do, you know, to bring the patient back every other day or whatever.

And the PRO instrument, I think, does have to be validated because patients assess themselves differently than we assess them. And so we don't really know what that means yet. It could, potentially be very helpful. It could actually potentially facilitate these kinds of studies. But I just don't think we know that much about the instrument yet.

ACTING CHAIR TOWNSEND: Dr. Fleming and then Dr. Kauffman.

DR. FLEMING: Well, just reiterating. The measures that we would use here would be, I would hope, somewhat inclusive in that it would capture the

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elements that again the IDSA document referred to. Fever, cough, pain, dyspnea, fatigue. So it should be a measure that if we are saying, Bob, feel better, it should be a measure that represents what a well developed instrument would capture. And feeling better is easily stated.

But to be reliably validated, this is the devil is in the details. And there has been, as you well know, an emerging science all across disease areas as people have worked toward trying to ensure that we have a validated assessment. And so those tools do have to go through construct validity, criterion validity, context validity, etcetera types of criteria to ensure that we are getting a reliable assessment of treatment effect. That is what the PRO is all about.

So, I think there is a strong endorsement that in these mild patients, there would be an appropriate emphasis given on resolution of the symptoms, where it is an

array of symptoms, but in a way that is reliably determined.

ACTING CHAIR TOWNSEND: Dr. Kauffman.

DR. KAUFFMAN: I would just make a comment. The reason I brought up the physician end of this is if you want to do any time analyses, time to defervescence, time to pulse and respiratory rate becoming normal, you really need objective criteria. You don't need the patient telling you that or the nurse talking to them on the phone. So, I think you build into the study enough money so the patient can come back and do a quick visit in your office. So it is not like standard business is going to be a little more careful follow-up of patients.

ACTING CHAIR TOWNSEND: Dr. Calhoun.

DR. CALHOUN: I was just going to mention that I agree with Dr. Patterson on the notion of making sure that the measurement

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instrument that you use gives you informative, gives you reliable information. But I am not sure that the instrument has to pass a formal validation test in order for you to be able to do that. You know, the asthma community will oftentimes use an instrument and analyze it with a delta delta kind of approach, so that we take the difference from beginning to end of the trial on both sides and then look at the comparison.

And in that way, many of the biases that might otherwise be there, that is, that patients rate their symptoms differently, will wash out because, presumably, there is some internal consistency in their response, in the way that they rate their symptoms.

DR. TEMPLE: We need to understand this. What I heard from the early part of the discussion here was that these weren't going to be people with a little touch of something. They are going to be pretty sick people who you determine could be treated as outpatients

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because they don't look desperately ill yet. So, the endpoints for improvement and success ought to be pretty similar to the ones we were using before, although you obviously don't expect these people to die or you would have brought them into the hospital.

So, this isn't sort of SF-36 kind of stuff. It is major symptoms and problems of their pneumonia. And clinicians ask about those all the time. I agree, we don't always ask that you validate someone's coughing scale. And my assumption is, if these people are being treated as outpatients, somebody is going to talk to them fairly often, otherwise they are -- but again, I need to be sure you agree on this.

What I heard is that people think the data we have on severe illness is probably now applicable to people who aren't necessarily hospitalized anymore because the modern world makes that unnecessary. But that really means they are fairly sick, have severe

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disease and we are not talking about things that you would ordinarily think of as just really mild. They have got a problem and everybody thinks it needs to be treated.

Are we hearing you right? Because that is what I heard or that is what I thought I heard. Maybe that is what I wanted to hear.

ACTING CHAIR TOWNSEND: I think there is a mix. You know, a lot of the patients they say are going to be like the patients that were studied 60, 70 years ago but a lot of them will have fairly minor symptoms and not feel well. So, it depends on how the study design is enriched to get the more sick patients in.

DR. TEMPLE: Yes, because we are going to try to get bacteriological evidence. They are going to be pretty sick.

ACTING CHAIR TOWNSEND: Right.

DR. TEMPLE: Just not so sick they have to come in.

ACTING CHAIR TOWNSEND: Dr. Wong-

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Beringer?

DR. WONG-BERINGER: I just want to say, echo the points that were made. And that is, the instrument, the PRO does not need to be validated now for us to start using them. But I think to use it, we need to also combine it with getting objective data from physician or nurse visits, a health care professional who can then compare the responses at the same time. I think there is validity in both and both need to be accounted for.

DR. VENITZ: I just wanted to add, number one, I agree with you, Dr. Temple, that I think some of those patients, at least, are going to be pretty severely ill. That is why I made the comment earlier. They may have to be visited as opposed to calling in. And that should be part of the assessment of the clinical success or failure. They may be defined for the most severe case.

The main reason, or one of the reasons, at least, one of the major reasons

why I believe that that should be the important outcome because that allows us to stay within the paradigm of thinking all this back to the studies 60 years ago. And I am personally willing to make the transition from mortality to success. I, personally, am not willing to make that transition from mortality to PROs. Okay?

So that is why my suggestion is, PROs, if they are used, they might be secondary endpoints. And maybe after we gain experience with it, turn into primary endpoints. But at this stage, I don't think we are there yet.

ACTING CHAIR TOWNSEND: Dr. Rex?

DR. REX: Maybe it would helpful to recognize there are two kinds of PROs. There is PRO with a capital P, which means that we have studied it like crazy and we have psychometrically validated it and we have wrapped a ribbon around it. And we believe you can translate it into French, German, and

Japanese, and you get the same result. That would be a PRO with a capital P.

And then there is the little version, the lower case P, where you do something that makes sense but maybe it only makes sense in English, but you know, it makes sense.

And again, I would say that I sort of liked that Nicholson oseltamivir versus placebo study. If you don't know it, this is the study where for influenza they said, maybe they gave them a card, I don't know, but twice a day the patient had to answer, there were six symptoms that I think they picked out of a textbook, as best I can tell you. You know, good symptoms in influenza, scratchy throat, runny nose, and stuff like that. And you had to say four times a day, was it absent, mild, moderate, or severe. And then they took your cards at the end of the observation period. And response was the first 24 hours when you checked absent or mild for everything.

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And did they psychometrically validate that? I don't know. I don't have the paper in front of me and I don't think they did. But does it make sense? Yes. And were they motivated to do it because they got something out of it? Sure, they were able to say we made you better 29 hours faster. I remember seeing it say 29 hours. And that is good.

So, in the case that we are talking about there, outpatient community-acquired pneumonia, what is the point? It is that we do have to start with existing paradigms. I can't go and invent something brand new because I don't really know all that much about it. I need to work with the kinds of things that have a familiar quality to them. We need to start with existing paradigms. And we do have, Dr. Venitz has said it well, we have a sense that even though you are not terribly sick right now, we know that in your lung you have an airspace filling

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bronchopneumonia that is bad news if left untreated. So we believe there is a big treatment effect.

And if you turn around from that, you continue to improve, we are saying, the dog that didn't bark, we have kept you out of a lot of trouble. But we didn't do it with a capital PRO, we did it with a little PRO. But I am, as a sponsor, motivated to explore. Again, why? Because I might be able to get something useful out of it.

So keep that in mind. It is not an official rule but it is the way medical commercial stuff works. If I want to show a little edge for my drug, I am going to be looking for something like this to put into it. And you know, you can say that that is the downside of the business, but is also the good side. It is going to drive me to innovate. It is going to drive me to work the FDA to come up with measures that could work.

And if we can validate a capital

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PRO, great. But don't make me have to do that just to get going. The little PRO that makes good sense, if it makes good sense to me, it makes good sense to my advisors when we are starting a trial, it will probably make good sense to everybody else.

ACTING CHAIR TOWNSEND: Dr. Patterson.

DR. PATTERSON: Well, I don't think it needs to hold up studying this disease entity. But I just think, you know, questionnaires, and I haven't been involved in clinical research myself, it can make a lot of difference on who is administering the questionnaire, how the questions are explained. And we talked about an example this morning of that Lamping paper. You know, the patients may not think of fever, but they do know what chills and sweats are. So that is what, that may be their fever equivalent. Fever may be the wrong question for them.

The same thing as what we would

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assess as dyspnea or shortness of breath, they may not call it that. They may say well, you know, I used to be able to walk to the mailbox but I haven't been able to.

So, I do think that this is a potentially very useful tool, but we do need, if we really are going to use that as our main assessment tool, then it does need to be validated. However, I don't think that it needs to hold up these kinds of studies because we can still evaluate patients like we always have.

ACTING CHAIR TOWNSEND: Dr. Fleming?

DR. FLEMING: We are encountering a very important issue here. And with its importance, i.e., trying to be able to document and validate what is the effect of an intervention on important symptoms, it isn't surprising that this is a challenge that we are encountering across many disease areas. And there is a science that has emerged for

this. And FDA has a guidance on what our key criteria for validating such instruments. I don't know that we have an expert around the table. We are doing a lot of discussion right now about how rigorous do we need to be in the validation of PROs. I am not an expert. I don't know if any of the rest of us are experts but I would be advising the FDA to ensure that you have counsel from experts in this area before we would draw a conclusion that it is really not all that important to be rigorous here.

Experience has indicated in many other areas for reasons that Jan, in part, touched on, that the devil is in the details here. And how you actually phrase the questions, how they are administered, what the questions are, these play a major role in the overall rigors of this. And there is a science on this. And I don't know that you have representation on this committee of the people that are the experts in that particular

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area.

And so, it is important that this be assessed because this isn't simply a case where it is crystal clear. And I had given some references yesterday to Medley's comment that median time to resolution of cough is 14 days, 20 percent of people would have substantial fatigue at three months. It is not going away, even under therapies.

There is, there are subtleties here and the bottom line is, I think there is a lot of consensus that we believe in the importance of addressing affects on symptoms. And that has multi components to it. Maybe what we are quibbling about here is what is the level of rigor that we have to have in formulating that instrument? And my point is, there ought to be people, psychometric experts and other experts weighing in on that because they have particular expertise relevant to this issue.

ACTING CHAIR TOWNSEND: Dr. Kauffman.

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DR. KAUFFMAN: Just a comment that I think in order to enrich this for people who truly have bacterial pneumonia, it depends on what patient population you go after and, if you go to a place like VA hospitals, you are indeed going to have lots of older men who have pneumonia because they have underlying risk factors for that.

If you go out to private offices and do these studies, you are going to have younger people, you are going to have more mycoplasma and viral disease kind of infiltrating into this.

So, I think aiming toward a population that is going to have a greater risk is going to be very helpful, too.

ACTING CHAIR TOWNSEND: All right, thank you. Dr. Temple?

DR. TEMPLE: Well, I mean the translation of the outcome data from the past requires a fairly sick population, as you said.

And I don't think this is going to be, you know, how is your cough. These studies will define a failure criteria, just like the ones in the more severely ill people will. And there will be things like, you know, it doesn't go away, if you are still febrile, you had to come into the hospital, all those same kinds of things, which if I understand everybody, is the real basis for saying that you know what the non-inferiority margin is. Once you get into much milder disease and that really isn't bacterial and stuff, I think it becomes very hard to say how we are going to picking on inferiority margins.

So, what I heard, and I think Dr. Venitz said it particularly, this is the modern era and those people who used to go the hospital and be really sick now get treated as outpatients. And that is fine. That means, if I understand it, that we can use those previous fairly convincing data on

effectiveness to apply to these populations. I don't think that is going to be about an SF-36, though. It is going to be about, you know, the nasty outcomes of failure.

So, I think we hear that. And unless I have just put words in everybody's mouth, I think we are pretty happy with that. Aren't we?

ACTING CHAIR TOWNSEND: Dr. Musher.

DR. MUSHER: Actually, Dr. Temple, I don't think that is correct and let me say why.

What I said before is if you went with pneumonia to a doctor, in the old days you are put in the hospital, even when I was an intern, you came with any kind of pneumonia, you were put in the hospital. Absent treatment, you would get worse. But at the time that you came in, it wasn't necessarily severe. So the severity business relates to the progression and the absence of treatment.

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As far as the likelihood that someone with PORT, so-called PORT score severity index group one or group two, I think the data are published. It seems to me that two percent or three percent of those patients end up needing hospitalization. And that is the way the data were presented in the New England of Medicine. It might two percent for the group two and it might be six percent for group three, and the mortality was under one percent for groups one and two and it may have been two percent or two and a half percent for group three.

The point is that you are dealing with a very tiny percentage. So you have to have a vast study to make those different and that is why you have to look at these other things.

DR. TEMPLE: But is what you are describing how they do with treatment?

DR. MUSHER: Yes, that is exactly right.

DR. TEMPLE: That is okay. What we are comparing how they do on treatment with is how they would have done if you didn't treat them.

DR. MUSHER: Well that is what you are comparing them to but I keep saying those data aren't relevant.

DR. TEMPLE: Well, if they are not relevant then you cannot say yes.

DR. MUSHER: That is why I agonized over it.

DR. TEMPLE: But fortunately, everybody else thinks they might be relevant.

DR. MUSHER: Yes, well, remember I began by saying I disclaim the opening paragraph --

DR. TEMPLE: Well, I know.

DR. MUSHER: -- because I think you can't say it and I think all of this discussion shows that you really honest to God can't tell. So, it is wishful thinking to think we can make some statement about our

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patients now and how that relates to the 1930's. You can't tell.

ACTING CHAIR TOWNSEND: Which makes a very nice segue into --

DR. TEMPLE: Well, that is always possible.

ACTING CHAIR TOWNSEND: -- the next question, if there is no more discussion on that one. "What is the proposed non-inferiority margin and what data support the proposed non-inferiority margin?"

Dr. Venitz?

DR. VENITZ: I do think we can use some of the information that Dr. Fleming presented, breaking down the mortality differences by severity and I think age, in particular.

And then I like Dr. Calhoun's suggestion to use the relative risk to scale it down, depending on the outcome and severity of the population that is being studied. So, I do, again, to answer your question directly,

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I do think this is going to be a more severe population than has been studied in the past. But I still think it is going to be predominately on the mild side. So you do have to scale it down. It won't be the same, I don't believe so, as it would be for the inpatients. And as a scaling factor, as I said, I would use a relative risk.

ACTING CHAIR TOWNSEND: Dr. Rex?

DR. REX: So, the exam question. Remember my benchmark statistical thing, 250 patients per arm, control has a 90 percent response rate. And so let's pretend we do a study of outpatient CAP, where there is a good clinical syndrome and I get a good microbiologic footprint a third of the time.

So, it is, we have some enrollment criteria that sound a lot like a typical bacterial pneumonia. I do my study, 250 patients per arm. I have microbiologic proof in let's say a third, let's be specific. And the active control, I used a quinolone, gave

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a 90 percent response rate. And new drug gives, let's say an 87 percent response rate. And that is 87 percent plus or minus six. Excuse me, it is a three percent difference, plus or minus six. So, it is within minus ten percent. Is this, and it is not the only trial you do, but it is one of your trials and it is done in outpatients as described.

Do we pass? Is that trial, as a piece of the totality, are you feeling good?

DR. FLEMING: Is your question well-defined?

DR. REX: The outcome --

DR. FLEMING: The outcome --

DR. REX: Yes, I'm sorry. Excuse me. The outcome is the clinical response outcome that we have been using all along, which is the collected sense, let's take it exactly like out of the Pertel paper. You got better. There is no further requirement for other therapy. You didn't have to switch drugs. I mean, it is the typical historical,

it is the typical clinical response that we have been using all along. And it is very much the same for inpatients as it is -- actually it is. It is the same for inpatients as it is for outpatients. And I am posing to you the exam question for the outpatients I am describing because that is kind of the results you would expect to get.

And I forgot to say, there is a one and a half percent, you know, a one or two percent mortality rate in both arms. There was a tiny, maybe it one percent, one person, two people died.

So, essentially no mortality. It is all based on clinical response. You have got a 90 and an 87 and it is the same kinds of clinical endpoints we have been using. That is what the exam question is going to look like when it comes in. Right? That is the exam question.

And I guess I will say that I think that given what we know, if those people,

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really young people even, with pneumococcus, I know that they were going die if they didn't get treated, so there is a huge treatment effect that is hidden on the other side of my quinolone comparator. And I have come very close to my quinolone comparator, so I am going to argue that that looks pretty good to me.

DR. FLEMING: But you are saying in this cohort that is going to have a 90 percent success rate, now you have just said I know they are going to die. They are not going to die.

DR. REX: Untreated.

DR. FLEMING: Untreated, they are not going to die. Not certainly all of these patients or even the majority of these patients aren't going to die in the absence of therapy. A lot depends on exactly who they are and how well they are selected. But when you define a 90 percent success rate, of course, that also depends on the exact nature

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of the measure. Is this a sensitive measure for any unresolved disease and a success-only complete resolution? I mean, what is -- again, the devil is in the details. What is the outcome measure you are using here?

DR. REX: Yes, success is --

DR. FLEMING: And is it 14 days after the end of therapy, in which case there is lesser ability to really talk about whether what you are doing is hastening or shortening the time to resolution?

Again, there is a lot of issues here that you are presuming are still perfectly appropriately addressed using the old measures of the past, which I didn't hear the IDSA endorsing the old measures of the past. So, when you talk about the non-inferiority margin, it depends on what the measure is. If the measure is going to be, as IDSA had indicated a measure that is looking at fever, and fatigue, and cough, and pain, and dyspnea and those are measure that when

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you look at them don't go away in a reasonably short time period in all patients, then I don't know that the answer is 90 percent is what the success rate will be in the control arm. If we use what has been done in the past and we select patients that are pretty pristine and we have the bias that what is going to make things look good is when in doubt call someone a success, then we would be translating to the 90 percent.

But I am not hearing the IDSA and at least a number of the rest of us saying, we are advocating just using the same measures we have had in the past. Therefore, the margin depends on the measure.

DR. WHITNEY: So just to get back to my earlier thought, I think the idea is that we would choose the margin that is as small as possible and you can sort of really ignore the historical stuff, if that is your goal, use the margin that is as small as possible, it gets you away from that

historical uncertainty.

I think if are looking at an effect that is 90 percent in the control arm, you can use that sample size and get that ten percent margin. And I think that if you are looking at an effect that is probably closer to 50 to 65 percent, and there is some in this IDSA table, that is when the margin has to get bigger.

Again, it is based on, you know, what can we do that is feasible that drives that margin as small as possible but yet doesn't delay the licensure of these drugs?

ACTING CHAIR TOWNSEND: Dr. Temple?

DR. TEMPLE: You can't ignore the historical experience. If you manage to put into your population 100 percent of people who would do well no matter what you did, then your trial is uninformative, no matter how small you make the margin. You have to believe that some of them wouldn't have done well. And your best estimate comes from the

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early unpleasant era where we didn't have good treatments.

So, how that needs to be modified for these people who obviously are not as sick as all of the people who were studied, is a great debate. But what I heard early, which is probably what I wanted to hear, is that you are picking people who are relatively sick so that those old data will appear to be reasonably applicable, that there would have been a substantial number of people who didn't do well and the treatment improved them by, I don't know, 15, 20 percent, the same numbers we are all working on. But if you really put in people who didn't have any disease, that would defeat the whole purpose of this. You wouldn't learn anything. You couldn't.

ACTING CHAIR TOWNSEND: Dr. Whitney.

DR. WHITNEY: Yes, no, I am saying you need to enhance for those people that would do poorly if they were not treated. But

you still can't use that historical thing as being anything that is directly translatable and quantifiable with any sort of certainty, given the different conditions today.

So, I think again, we should try to shoot for the margin that is as small as possible, taking into account that you have enhanced for patients that really need antibiotics.

DR. TEMPLE: So are you suggesting that in this setting, since we are not sure how big the effect is, we should be going for like five percent as the M2? That starts to get to be a very big trial.

DR. WHITNEY: Well, no.

DR. TEMPLE: But maybe that is the right thing to do.

DR. WHITNEY: No, just, I think you know, we have batted around 10 percent when you have got an effect size around 90. But when you are looking at some of these other effect sizes that are closer to 65, 50

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percent, I think your margin has to get above ten.

DR. TEMPLE: Well, yes, the margin here is the difference between a treated and an untreated group. So the stuff Tom showed was that this was on mortality. It differed by about 20, actually some estimates were larger.

If these people aren't quite as sick, you could imagine that the difference will be not quite as big as that. But I thought the idea was to pick people who, even though you are going to let them walk home, are plenty sick, have a high likelihood of pneumococcal pneumonia and have a reasonable chance of not doing very well. Not so different from the historical experience.

In that case, if you believe all that, that could make the argument for using the same roughly 10 percent non-inferiority margin as your M2.

ACTING CHAIR TOWNSEND: Dr.

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Wiedermann?

DR. WIEDERMANN: Well, and that said, I am very confused. And I think I heard Dr. Temple, especially just now in the discussion with Dr. Musher, if the decision is that there are plenty of patients in those historical trials who would have been treated as outpatients today and, therefore, we can use that database to inform our current studies. But, we don't know within those groups who was mild moderate versus moderate severe, then we have to use the same M1 and M2 that we are using for our moderate to severe group. Because nothing else makes sense to me.

DR. TEMPLE: Yes, that is what I thought people were saying before, that that is our best guess and we are going to try to get sick people a lot like, I mean, Dr. Venitz said it, it is clearly a lot like those people who were in those other trials but this is now and so we don't put them in the hospital. But

they are still sick. They still do badly. They have a high likelihood of growing a pneumococcus. So, those old estimates are reasonable to apply to them. You know, perfect knowledge, we don't expect.

ACTING CHAIR TOWNSEND: Dr. Patterson?

DR. PATTERSON: Well, I was going to say 10 to 20 percent, based on what I said for the first series of questions. But because this group would look at severity of one through three or perhaps four, instead of two through five, which would be in the other, the severe group that we were talking about before, you know, it may be closer to the ten percent but I would still say 10 to 20 percent.

ACTING CHAIR TOWNSEND: Dr. Musher.

DR. MUSHER: I am still sorry that all we are looking at is some final decision on clinical outcome. I still think that we should be able to design studies that look at

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the rate of the improvement in the various parameters that are being followed. And I just think that needs to be emphasized.

ACTING CHAIR TOWNSEND: Dr. Kauffman?

DR. KAUFFMAN: I think that is still legitimate, Dan, but I think the 10 percent makes sense. You know, if you are going with the same database, then I --

DR. MUSHER: My comment didn't deal with the 10 percent.

ACTING CHAIR TOWNSEND: Dr. Rex, did you have something to say?

DR. REX: I always have something to say. The question is whether it is worth listening to or not.

Bob Temple has, you put your finger on it. It has got to be a good syndrome. You have got to have a reasonable degree of microbiology and that is then, by definition, not a trivial disease. A pneumococcus in your lung, airspace filling, bronchial pneumonia,

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no matter how you feel right now, that is a bad thing. And I think that is the biologic perspective from which I argue. You know, you might look pretty good right now and I am glad you look good and I am glad you continue to look good. And I can capture that with the clinical, with the kind of clinical endpoint we have been using for the past 15 years.

Now, can I do better? I can do better, Dr. Fleming. I am going to work on doing better. But can I do better this afternoon for the purposes of starting a clinical trial program or for telling people how they could plan to start a clinical trial program? No. I am going to have to work from within existing paradigms. We will gladly work incrementally over time to improve our ability to measure more accurately or more precisely.

But we do need to start from existing paradigms and I think we have enough data to support the concept, basically, as Dr.

Temple laid out, of a clinical response measure with, it is about a ten percent margin. And that is well reasoned from the historical database.

ACTING CHAIR TOWNSEND: I think, unless there is -- go ahead.

DR. FLEMING: Well, I just, I struggle here because, obviously, there has to be a clear formulation of what the exact measure is to begin to talk about what the non-inferiority margin is.

I endorse Dr. Musher's point that there is a lot of information here beyond at test of cure, some extended period of time later. There is a lot of information here about the timing of resolution. And as long as one is looking at this in a fairly comprehensive way across the various symptoms that matter to patients and look at it across time, as Dr. Musher has advocated, that to me makes a lot of sense.

Now, my concern is, that is very

different from the clinical test of cure assessment that we are doing at this point. And it isn't going to be as simple as 90 percent of the people are going to be success and now we can have a 10 percent margin to rule out a doubling in that failure rate. And once we have such a measure that is more comprehensive, is it possible to formulate, and I don't know how to call a margin here because I don't know what the statistic is that you are using to aggregate that event, that evidence. It is probably not success/failure. It could be success/failure but probably isn't.

And so we have to get there first before we can really start talking about what the margin would be. But let me just throw out a concept. If we could get there with something that really is more comprehensive and valid in assessing how we are impacting patients' symptoms, then is it possible to ask for something a little less than superiority?

Now, if I knew a dichotomous outcome, that would be sort of what Bob Temple is talking about. Maybe it is a five percent margin. But that is a real accommodation in the absence of historical data to truly validate what is the effect of the active comparator on that measure.

But it is also entirely possible that with an enhanced sensitivity that you are going to get when you are looking over time, as Dr. Musher says, and when you are looking in a more comprehensive way, we may have a lot more sensitivity discerning differences between these interventions. We may well be able to actually to have some sensitivity to something that is a little bit better. And when you are a little bit better, you can rule out you are a little bit worse, without an extraordinary sample size.

ACTING CHAIR TOWNSEND: Thank you. Dr. Rex?

DR. REX: I agree with what you

say. I do. And as a sponsor, I am motivated to try to develop those tools. But I also live in the real business world and I need a path that I understand now. The industry needs a path now that it understands and a path that is not foolish. A path that is supported reasonably well. Life, you know, is such that I need to be able to --

Yesterday, we had a wonderful slide about predictable. Predictability is not stacking the deck in your favor. Predictability is knowing a set of rules that I need to work against and knowing that they are not going to change too -- knowing that they are either going to remain stable or how they are going to change, but being able to work within that framework over time.

That is really what we are asking for. And we have had a system up until now that has got some issues, clearly, but it is not grossly broken. And we have actually dug deeply into the data and, to our delight and

surprise, we find that what we have been doing is actually better supported than we thought. I mean, there is a lot of deep rationale behind this. And so, you know, however we came about these things before, it was pretty good work.

And now that we have beaten through it, we do find that there is, you have got to take everything, though. And it is not any one piece. You have got to take the biological plausibility. You have got to take some statistical thinking. You have got to, you know, all we have learned about pharmacokinetics, it is all wrapped up together.

There is no one -- if all I showed up with was one bit of data, you should throw me out on my ear. But I am not showing up with one bit of data. I am showing up with an entire very dense package.

DR. FLEMING: There isn't consensus but I guess that is obvious now. There is not

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consensus on what you just said.

ACTING CHAIR TOWNSEND: Thank you. Let's go ahead and move on to 2(b). And again, this is a yes or no question. So I will ask the question and then we will go around and ask for the yes votes and then the no votes.

"Can placebo-controlled trials be carried out in less severely ill patients with community-acquired pneumonia? If yes, how can risk to patients be minimized? What patient population could be enrolled and what endpoints should be evaluated?"

We will start off with Dr. Whitney. Raise your hand if you say yes to this and then we will start with Dr. Whitney, if you are a yes vote. If not, we will move on. Do we have any yeses?

(Show of hands.)

DR. MUSHER: I move that we move on.

(Laughter.)

ACTING CHAIR TOWNSEND: Raise your hand if you vote no.

(Show of hands.)

ACTING CHAIR TOWNSEND: All right. And if everybody could go around. Dr. Whitney, state your name.

DR. WHITNEY: Cindy Whitney, no.

DR. FOLLMANN: Dean Follmann, no.

DR. WIEDERMANN: Bud Wiedermann, no.

DR. FLEMING: Tom Fleming, no.

ACTING CHAIR TOWNSEND: Greg Townsend, no.

DR. KAUFFMAN: Carol Kauffman, no.

DR. CALHOUN: Bill Calhoun, no.

DR. VENITZ: Jurgen Venitz, no.

DR. PATTERSON: Jan Patterson, no.

DR. MUSHER: Daniel Musher, no.

DR. DOWELL: Scott Dowell, no.

MR. MAKOWKA: Ken Makowka, no.

DR. WONG-BERINGER: Annie Wong-Beringer, no.

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ACTING CHAIR TOWNSEND: Thank you.

EXECUTIVE SECRETARY MOSADDEGH: All right, it is unanimous 13 nos. Thank you.

ACTING CHAIR TOWNSEND: Good. C, this is again yes/no. The same procedure.

Can you suggest any alternative -- actually this is not a yes/no. This is just not a vote question, just comments if you have any. "Can you suggest any alternative study designs that could be utilized which would allow for an informative trial of outpatient CAP that is an oral drug to be conducted? If so, please describe."

So, if you have any alternative study designs.

DR. MUSHER: Just in one sentence. I have said that we should follow the rate of improvement using several parameters. Dr. Fleming echoed it a few moments ago and I think that those should be studied and developed.

ACTING CHAIR TOWNSEND: Dr. Venitz?

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DR. VENITZ: I was just intrigued by one of the backup slides in Dr. Goldhammer's presentation where he talked about effect retention likelihood as an alternative to the non-inferiority trial. So, I throw this out. I have no clue what it is, but it sounds like it is something that is used in oncology dealing with the same issue, not being able to use placebo controls.

ACTING CHAIR TOWNSEND: Dr. Follmann?

DR. FOLLMANN: I would like just to talk briefly about the Lade initiation trials. And so one thing you could conceive of doing would be to have a standard non-inferiority trial where you compare a standard to experimental. But within that also randomize another factor, which would be immediate treatment versus delayed treatment of maybe four hours or so.

I don't know if the stars will align and if you use rapidity of response or

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defervescence as an endpoint for the delayed question or not. It is just something that I would suggest we consider and run the numbers on.

But getting back to that design, you could compare the two groups in terms of non-inferiority on your mortality or clinical failure endpoint. And after you had done that, you could look within the experimental arm and to see is there superiority in terms of time to defervescence or rapidity of symptom relief within the new arm, early versus delayed. So, we will see what the numbers -- whether that can in fact happen.

In the last two days, one thing that sort of dampened my enthusiasm for such a study is that really a delayed response trial is asking the question really of what is the effect of the drug compared to placebo, when we are not actually doing a placebo, we are just withholding therapy for a few hours. And so, if that is a clinically relevant

question, this design might have some merit.

ACTING CHAIR TOWNSEND: Bob?

DR. TEMPLE: Well, Dr. Musher would say that during that first four hours, the ones who don't get the drug should get a placebo. But leaving that aside, so it really is --

DR. FOLLMANN: Well, I would agree with that.

DR. TEMPLE: -- a placebo controlled trial. We strongly, me, in particular, have advocated that in some of the areas where people thought it was ethical to delay therapy, you know, maybe otitis, things like that, wait for a couple, compare early and late.

I have to say, I got the impression from most people here that they would not countenance such a delay in somebody who was thought to have, you know, bacterial pneumonia. And so, I don't know. Does everybody think we could actually do that?

That anybody could do that?

DR. FOLLMANN: Well, let me just, before the other people speak, and I was imagining this in a population that had a one percent mortality rate or something like that.

And I would also mention that I used to work at the Heart Lung and Blood Institute where there would be trials which would look at different targets of systolic blood pressure or cholesterol level. And sometimes these targets had been not on clinical trials, but on expert consent, sort of the view of the community and that is not really randomized trial evidence. And so you could make an argument there if you have non-evidenced based guidelines, maybe delayed or immediate treatment or an LEL or whatever, you could legitimately look at that in a randomized trial.

ACTING CHAIR TOWNSEND: Dr. Rex.

DR. REX: The problem with delayed therapy, from a physician standpoint, is that

it is really hard not to get somebody to therapy when they could be sitting there being bacteremic and there is a lot of impetus in the Medicare reimbursement, the rules in hospitals to start therapy. Probably it would be really hard to go up hill against that. In the sponsor community, where we look worldwide, we are faced with just a great antagonism against any kind of a delay in therapy.

Because I am sensitive to what you are saying. It would be a nice thing to do if we were talking about toenail infection. We are actually talking about, we are talking about the lung, which is a place where if the pneumonia gets out of control, you can quickly progress into sepsis, particularly if you are talking about Dr. Kauffman's older patients at the VA.

So I think it is really, it is not -- to ask the sponsor community to do that is, as Dr. Talbot said, that is not the kind of

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study that we can drive forward. That might be an investigation that could be done in another setting, but that is not something that we can deal with. So, that is my comment on that.

My suggestion for a design is to be sure you collect some good PK data to see if we can get some more exposure response stuff for Dr. Tourneau.

ACTING CHAIR TOWNSEND: Dr. Venitz?

DR. VENITZ: I serve on an IRB and I doubt that you will be able to get permission for a study like that. A potentially fatal disease, even at less than a one percent or two percent mortality and you are delaying effective treatment for four hours, I don't think that is ethical.

ACTING CHAIR TOWNSEND: Dr. Kauffman.

DR. KAUFFMAN: I would just make the comment, the patient wouldn't understand

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what you were doing. Please sit here for four hours and then I will give you your medicine. So, they won't agree either.

ACTING CHAIR TOWNSEND: Any other comments on that question? Oh, Dr. Calhoun. Sorry.

DR. CALHOUN: Well, the other thing is that there actually is some evidence that early implementation of antibiotics has a beneficial effect on outcome. And so to ask that question with a four hour delay or a six hour delay, I am not sure that we would get information that would be particularly helpful in understanding what the versus placebo response actually would be. I think it is predictable that there either would be no effect if the tool weren't sharp enough, so to speak, or that you would see a negative effect of delay of therapy, based on the evidence that we have got so far.

ACTING CHAIR TOWNSEND: Thank you. All right, we will go ahead and move on to

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question three. Again, this is not a yes or no question, so we will just go around.

"In a setting of hospitalized community-acquired pneumonia, as described in question one, one could study therapy with an intravenous formulation administered initially with subsequent 'step down' therapy to an oral formulation as a means to support the use of the oral and IV formulations for a severe disease. This leaves the question of whether the finding of efficacy for severe CAP would provide evidence of efficacy that could be used to support efficacy of the oral formulation for less severe, that is, mild to moderate CAP." I guess this is, actually, a yes or no question. "Do you believe the finding of efficacy in more severe CAP supports the drug's effect in less severe CAP, even though the drug has not been directly studied in less severe CAP?"

This is again, a yes or no question. If you believe that you can

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interpret studies in more severe CAP to apply to less severe CAP, the answer is yes. Otherwise, it is no. Raise your hand, please, if your answer is yes.

DR. WIEDERMANN: Can I get a clarification?

ACTING CHAIR TOWNSEND: Certainly.

DR. WIEDERMANN: I just want to make sure we are talking about the same drug, just different formulations.

ACTING CHAIR TOWNSEND: That is yes. Again, if your answer is yes, please raise your hand.

(Unanimous show of hands.)

ACTING CHAIR TOWNSEND: If we can go around, Dr. Wong-Beringer?

DR. WONG-BERINGER: My answer is yes, I think mainly this, if for nothing else, it should be an incentive for industry to conduct trials in enriching the population that we really need to know information in. And those are the severe pneumonia patients.

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ACTING CHAIR TOWNSEND: Mr. Makowka?

MR. MAKOWKA: I voted yes but I would also like to ask, if it is the same drug, why isn't it available for the severe patients in an oral form?

ACTING CHAIR TOWNSEND: Can you restate your question please? I'm sorry.

MR. MAKOWKA: Why aren't we waiting to test the effect of the oral form of the same drug on the less severe? Why not use it up front?

DR. COX: I can try and clarify. Do you want me to do it now or do you want me to wait?

ACTING CHAIR TOWNSEND: Go ahead.

DR. COX: So when we write these questions, we don't know quite where all the answers are going to fall out. So this provides another way to try and look at an oral drug and try and understand how we might assess efficacy in an oral drug. And if there

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is efficacy data from the IV formulation, we are just wondering, is that beneficial to us in understanding the effects of the oral drug.

So, I don't think that the particular scenario that you are describing is really what we are trying address here. We are just trying to understand how the efficacy data from an IV formulation could be translated down to an oral formulation of the same drug. So, they would both be available.

DR. TEMPLE: So you do the study in the very severe hospitalized people using both IV and then oral, but it would apply to less severe illness that might be treated with just oral, doesn't solve the I am only an oral drug problem.

ACTING CHAIR TOWNSEND: Dr. Dowell?

DR. DOWELL: Yes. So I said yes even though I don't believe it is completely true. By that I mean that I don't believe the etiologic agents are the same in severe hospitalized pneumonia as they are in

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outpatient pneumonia. I think it is almost certainly not going to be true and that the distribution of agents is different and, therefore, the effectiveness of the antibiotics is likely to be somewhat different.

But I am comfortable with a yes because I figured that if you are treating the things that are going to cause severe disease, you are preventing most of those outpatients from getting into bad trouble with the severe disease, even though you are acknowledging that you are letting slide a little bit the milder disease.

ACTING CHAIR TOWNSEND: Dr. Musher.

DR. MUSHER: Daniel Musher, I voted yes.

DR. PATTERSON: Jan Patterson, yes. And I think that as long as your severe population that you have studied has a broad spectrum of microbiological diagnosis that includes mycoplasma and MRSA, perhaps.

DR. VENITZ: I voted yes and my concern is the same as stated before. The microbial composition has to be the same or similar between the two populations.

DR. CALHOUN: This is Bill Calhoun. I voted yes. I had the concern that was articulated first by Dr. Dowell and shared by several others. The microbiome is pretty clearly different based on the severity. And so, to the extent that the microbiome is somewhat different, the applicability and the efficacy rates and so forth may be somewhat different.

But mitigating that concern is the fact that in contrast to some other disorders, hypertension being one which has many many many pathogeneses underlying, we understand the pathogenesis of infectious disease, an organism interacting with host defenses, etcetera, etcetera. So, although there is concern that the microbiome is different, I think that is mitigated a little bit by your

understanding that it is an organism that requires killing on the part of an antimicrobial agent.

DR. KAUFFMAN: Carol Kauffman. I voted yes. And the only thing I would want to see for sure is that the company studied the PK characteristics of the drug, so they are sure about absorption and serum levels and that sort of thing.

ACTING CHAIR TOWNSEND: Dr. Townsend. I also vote yes, with the same reservations as about possible differences in microbiology.

DR. FLEMING: Fleming. I voted yes and had similar thoughts to Dr. Dowell that I don't believe it is completely true. But, i.e., that it is completely appropriate to say we know that the effect can be extrapolated. But I do see it as an incentive to study more severe disease, which is critical that we do so. And I think it is a way forward to addressing the unmet need in less severe

disease before we have a more rigorous and appropriate way to do so with valid PROs.

Now, my interpretation of the yes is, if you have, for example, I don't care what it is, if I studied IV or oral, if I studied of the formulation of the agent in severe disease and showed non-inferiority on mortality, then I would support labeling that formulation in CAP for the reasons that were indicated.

Then for the opposite or alternative formulation which frequently would be going from IV to oral, then we would need a bioequivalence assessment to validate that other formulation. Now, again, I have a reservation about this but I see this as a tradeoff, as Dr. Dowell had pointed out.

But one of my additional reservations is safety. We have gone through two full days and we have not talked a lot about what is an adequate assessment of safety. And not all antibiotics are fully

safe. And Dr. Talbot's list of antibiotics in trouble yesterday certainly include antibiotics that are in trouble due to safety issues. And we need to ensure that in our pre-marketing studies, as well as our post-marketing studies, that we are doing adequate assessments to ensure that we are identifying safety issues.

And I have a little bit of concern then, if we are only studying severe disease, that we are going to extrapolate that to mild disease because everything is benefit to risk. The bar, in my view, is more lenient or higher as to what I would accept in a safety profile when I am doing something about mortality. In mild disease, if I am doing something about symptoms, while that is important, the bar becomes much lower in terms of what I am going to accept in terms of safety.

So, the FDA should ensure that the strategies that we are using are appropriately sensitive not only to establishing efficacy,

but ensuring safety.

DR. WIEDERMANN: Bud Wiedermann, yes. And I might suggest at least to consider with regard to the PK bioequivalent sort of argument, whether more stringent demonstration ought to be required, if a product pursues approval for milder disease with this kind of study design.

DR. FOLLMANN: Dean Follmann, I voted yes and I really have little to add.

DR. WHITNEY: Cindy Whitney, yes.

ACTING CHAIR TOWNSEND: Thank you. Question four --

EXECUTIVE SECRETARY MOSADDEGH: Just for the record, it is 13 yeses, unanimous. Thank you.

ACTING CHAIR TOWNSEND: Again, yes/no question.

"If the available evidence for settling a non-inferiority margin in current CAP trials is derived primarily from studies of patients with CAP due to Streptococcus

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pneumoniae, should non-inferiority studies include patients with other etiologies of CAP?"

Please raise your hand if your answer is yes.

(Show of hands.)

ACTING CHAIR TOWNSEND: All right, Dr. Whitney, if you could?

DR. WHITNEY: Yes, I voted yes because I think we have already talked about this. I think we talked about using pneumonia syndrome but trying to enhance for the bacterial components. So that would include strep pneumo but it would include some other things in there.

DR. FOLLMANN: Dean Follmann, I voted yes.

DR. WIEDERMANN: Bud Wiedermann, yes, with the same caveats. We need to break it down by agent.

DR. FLEMING: Fleming, yes.

ACTING CHAIR TOWNSEND: Greg

Townsend, yes.

DR. KAUFFMAN: Carol Kauffman, yes. Again, similar to what Cindy said, when you enroll patients, you don't know what they have. We try to select for pneumococcal disease and we will get mostly that. But there is no way I think you can study these other entities under themselves. And I think wrapping them into a CAP study is appropriate.

DR. CALHOUN: Bill Calhoun, yes, same reasons.

DR. VENITZ: Jurgen Venitz, yes.

DR. PATTERSON: Jan Patterson, yes.

DR. MUSHER: I abstained, but I would like to comment. I don't understand the question, interestingly.

Let's say we have a patient whom we are starting on a certain, let's say it is a quinolone which is not effective against staph aureus and we are comparing it to ceftriaxone and azithromycin. And let's say that the laboratory six hours later reports that the

sputum contains lots of gram positive cocci clusters and I don't know what we are supposed to do. And that is why I didn't vote. And I do think it is an issue you have got to deal with.

DR. DOWELL: Scott Dowell, I voted yes. I had the same concern Dan is raising about staph aureus. I think this has been touched on a couple of times in this discussion. But you know, in pediatric pneumonia, this is the big story right now. And that is what is being treated and we are really, a lot of this discussion has been directed at pneumococcal pneumonia but I think staph aureus is a big issue that hasn't fully been explored in these last two days.

MR. MAKOWKA: Ken Makowka, yes.

DR. WONG-BERINGER: Annie Wong-Beringer, yes. And I have the same concerns as Dr. Dowell and Dr. Musher.

ACTING CHAIR TOWNSEND: I think that was unanimous. Was it 12 yeses, one

abstention?

EXECUTIVE SECRETARY MOSADDEGH: Twelve yeses, one abstain. Thank you.

DR. MUSHER: Mr. Chairman, does that mean that others do not share the reservation that I have? A couple did.

ACTING CHAIR TOWNSEND: Certainly some did.

DR. MUSHER: I think it is a big problem.

ACTING CHAIR TOWNSEND: So we certainly had discussion.

DR. MUSHER: So that is part of the discussion part of it. The discussion part of the record shows it is a concern.

DR. FLEMING: Well we need, in fact, we still need to address the bottom part of this.

My answer for yes was simply that it isn't necessary that it be exclusively pneumococcal. That is what I understood we were asking. The question formally says,

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could you include other etiologies? Now, there needs to be discussion, I would hope, about the nature of what those other etiologies are.

My general sense about that is what I would hope is that we would have a preponderance of pneumococcal-like or at least a collection that would have similar pathophysiology, i.e., so if the intervention is one that we are using that has been studied showing an effect in a certain spectrum of bugs, that we would have some sense as to the degree to which this trial is being conducted in an overlapping scenario.

And I think, my sense is, there is a lot of flexibilities here in Haemophilus influenzae and Klebsiella but Mycoplasma, certainly Legionella are different and Chlamydophilia are different. I.e., my sense is we are somewhat looking at what I might call a more purely bacterial infection as opposed to something that is more viral like.

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And Legionella would be a concern because certainly we understand there is a different spectrum of activity there. So, my sense, my answer being yes was that we wouldn't have to be exclusively looking a pneumococcal, but it matters what the other components would be. And some of them need to be considered differently.

ACTING CHAIR TOWNSEND: Dr. Calhoun?

DR. CALHOUN: Thanks. Yes, relative to Dr. Musher's concern, clinical trials have to be conducted under the rubric of good clinical practice. And so I think that any trial, were information to come to light to the investigator that suggested that the regimen or regimens that had been prescribed for that particular subject was inappropriate, were there a suggestion that MRSA was a particular concern, I think then the investigator and the protocol would have to allow that that patient be put on

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appropriate therapy, that subject be put on appropriate therapy.

So, I think that GCP gets us a little room to work here, when you get data that suggests that what you have done empirically is not, in fact, appropriate.

DR. MUSHER: And similarly, if you are studying a drug like, I take an example, ceftobiprole, which is some advanced sort of a cephalosporin and the gram stain comes back showing no organisms and loads of PMNs, then you might say to yourself, that does look like a Legionella and I am going to go ahead and add something in the treatment of that, just as an example.

And if that is all covered, then I am perfectly fine just as it is. If we are all understanding it, that is fine.

ACTING CHAIR TOWNSEND: Dr. Kauffman?

DR. KAUFFMAN: You know, I was just going to add that community-acquired MRSA

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trumps everything and it speaks to diagnostics right up front as best as you can. You don't put those patients in the study.

ACTING CHAIR TOWNSEND: Except as someone mentioned earlier, if you have a drug that is effective against MRSA, you probably should have a comparator agent that is also effective against MRSA.

Dr. Rex?

DR. REX: Just very briefly, the other thing that would help you be comfortable with these organisms would be knowing that your preclinical data suggested that you ought to be able to treat them and that the PK target for them is the same as it is, say for the pneumococcus. And that would be something else that would help you be comfortable that the result was meaningful.

ACTING CHAIR TOWNSEND: Dr. Cox.

DR. COX: And just so folks know. We haven't talked about this too much, but typically the inclusion/exclusion criteria

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would appropriately define patients who would be appropriate for the study. If the antimicrobial spectrum doesn't cover a particular agent, then obviously, there would need to be provisions to address that.

The other issue is that typically what we are doing now is, we are looking at the syndrome. But then we also look at the microbiological data that we have from within the clinical trial to see the spectrum of organisms that patients within the trial had, looking for some minimum number of patients with each of the different types of organisms in order to include that in the indications and usage section. And that information is also then paired with what we know from preclinical data, whether that be in vitro studies or animal models of infection to get an understanding of how the drug works against particular genus of species.

DR. FLEMING: So just to come back to something I was alluding to, if we were

looking at Chlamydophila or Mycoplasma, I am more concerned about in those just showing something that looks non-inferior. If in fact we have less confidence that our agents would in fact, our active comparator agents would be providing benefit there.

In Legionella, if we were using a beta-lactam, then clearly I wouldn't be looking for non-inferiority, I would be looking for superiority. But with Legionaella if we have arithromycin or azithromycin as the active comparator, then we probably could come up with a non-inferiority margin for Legionella.

So, I think there needs to be that level of attention given, particularly if you are talking about trying to make a non-inferiority assessment for efficacy.

ACTING CHAIR TOWNSEND: Other comments? I know that many of the panel members have a taxi to catch at 4:30. I think if there is nothing more to be said, unless

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Dr. Cox has something to add?

DR. COX: I just wanted to thank everyone for all their participation. You know, it has been a very helpful two day meeting to us and I appreciate all of the discussion and all of the advice you have provided us.

Thank you very much.

ACTING CHAIR TOWNSEND: Thanks again. The meeting is adjourned.

(Whereupon, at 4:36 p.m., the foregoing meeting was adjourned.)