hospital already puts you in a pretty high category, if you have also got a high risk of a true bacterial pathogen.

So that is my comment on moderate severe. It is really enough, I think, to be in that category, based on everything we know.

I would also observe, in terms of mapping from mortality to clinical, you can't have a clinical success if you don't live. And so the mortality benefit is the actual minimum possible benefit that we can be dealing with because you have got to live to get going on this deal.

So I think Dr. Venitz made that comment and I just want to second that.

ACTING CHAIR TOWNSEND: Dr. Dowell.

DR. DOWELL: I want to reemphasize what several people have said, which is the PORT score is not enough. And the point to emphasize, I think, for the FDA is that the PORT score is applied to somebody who has community-acquired pneumonia but would

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encourage you to focus on the definition of community-acquired pneumonia, with these points in mind that the idea is to enrich for bacterial pneumonia. And so, before you do the PORT score, the way that you define community-acquired pneumonia may be one of the most important things that you do to enrich for those patients who actually have bacterial pneumonia.

ACTING CHAIR TOWNSEND: Dr. Temple?

DR. TEMPLE: When you say enrich for bacterial pneumonia, do you mean actually growing a bug or finding characteristics that make you think it is more likely that they have a bacterial pneumonia?

And I guess I would also add that one could enter a lot of people into a study. Of course, you won't know whether they have bacterial pneumonia yet and do the analysis only on the people who actually have a bacterial pneumonia. I mean, that means you have to recruit a lot more people because you

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seem to be able to grow something in only about 20 percent, but that is not impossible.

ACTING CHAIR TOWNSEND: Dr. Rex?

DR. REX: The industry view on that is that it is important that we think carefully about not being too insistent on 100 percent microbiology because that could easily cause the trial sizes to go up five-fold and that makes it not possible to do anything.

So I think I spoke, I didn't speak as clearly a minute ago as I should have. What it would seem reasonable and possible to do is first you start off with a clinical syndrome that really smells bacterial. And not guaranteed. It could still be influenza. It could still be a pulmonary embolism. Sometimes it will be a pulmonary embolism and sometimes it will be influenza. But if you start with a syndrome that is pretty typical, and thus the word typical versus atypical pneumonia. It is a typical pneumonia syndrome.

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And if we really work hard to find microbiology, which can be culture or urinary antigen I should think would be acceptable. And let's pretend that we do such a study and we find a microbiological footprint of some sort that was pretty strong in, I don't know, 30, 40 percent of the cases. We also have some data to suggest that we are going to have lost the signal in a few people because they got a little dose of some prior drug. We had the interesting study yesterday about if you do a transthoracic aspirate, not that I am suggesting that, I am not volunteering for one, but if you did it, you would find a bit more pneumococcus, if you are in a setting where the prior probability of it being bacterial is high.

So the suggestion that we have is that we are not asking to be given the whole 100 percent on trust that they are bacterial but rather that the collection of information, the syndrome is really sharply etched. It

looks very much like a typical bacterial pneumonia. In many people, we actually got a real bug out of them. This is a type of a syndrome that in the past has responded to anti-bacterial therapy, like the Agranat experience.

You know, go back to the Agranat thing. Even in the milder, the younger people, they saw a difference in their fever curve with an anti-bacterial agent. So that suggests it probably wasn't influenza. Because you wouldn't think that sulfapyrazine would move the fever curve on influenza.

So it is that collection of things. And it encourages us, as sponsors, to work on really good trial execution. We want patients that fit those criteria. We want our investigators to be well trained to get people that really could cough in a cup. So that is the theme that we are aiming at here.

If you force however that the final analysis, the only analysis that counts is on

the one-third for whom I have a bug on a plate, that is going to hurt a lot.

ACTING CHAIR TOWNSEND: Dr. Musher?

DR. MUSHER: How would you instruct companies? How would the FDA instruct companies and how would companies instruct investigators to try to select patients for a bacterial syndrome?

And by the way, I agree with you, there really are people who say you can't tell. But I really honestly do think that you can tell, in general. They are obviously bell-shaped curves but I think you can enrich by the clinical story based on white blood cell count and the clinical evolution and so on. I think you can do a lot to tell a bacteria from a mycoplasma or something else.

But how would you do that in practice, John?

DR. REX: You are asking me? You know, it's like bringing coals to Newcastle.

Dr. Musher, I have given you my

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suggestion, which is to say that the classic syndrome, you know, I read a little piece out of one of these papers, you know, it needs to be an abrupt onset of a febrile syndrome that points to the chest with a change on the chest x-ray and probably with the ability to produce some sputum that you weren't producing yesterday. You know, those things together suggest a bacterial etiology. And it is the abruptness, it is the acuity of the presentation. And if you do that, I am not going to guarantee that everybody has the bacterial coughs. There will be somebody in there who had a pulmonary embolism but on the balance, you are going to have been studying bacterial diseases enough so that you are going to have a pretty good signal out of this.

DR. MUSHER: Listen, I like the idea but I think a lot of it is going to end up in the culture of, and I don't mean bacteriologic culture, in the culture of how

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the study is taking place. In other words, the company and the individual investigators sort of have to get together and say we really want to have patients with bacterial pneumonia. So as you select them, please try to do thus and so because you can't put down on paper in general like this. And I don't think you want to put down on paper that you have got to have an acute onset because, as you very well know, a lot of patients who develop pneumococcal pneumonia, especially in the older population, they start with a viral syndrome and then they drift downhill for a few days and then it just gets a lot worse over a period of a day or two. But that is not the same as that so-called classical onset of the shaking chill, somebody who was perfectly fine until yesterday afternoon.

ACTING CHAIR TOWNSEND: Dr. Wiedermann?

DR. WIEDERMANN: So I can say this not taking care of adults with pneumonia but

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that there may be, so I don't know what list of criteria you can use but there are parallels to this, for example, in pertussis which is notoriously difficult to diagnose accurately. With the acellular pertussis vaccine trials, there were grades of definition of what a case of whooping cough was and then vaccine efficacy calculated for each of those definitions. And I would think by trying to look into that bell-shaped curve of signs and symptoms, you can develop a bit of a hierarchy for any clinical illness. And that might be valuable. Again, you can't prove it but you don't so limit yourself just to the culture positive patients.

ACTING CHAIR TOWNSEND: Dr. Rex.

DR. REX: I'm sorry. I seem to be hogging the microphone but let me answer Dan's question.

Let's just actually go to the Pertel paper, which I have pulled up, because it is a nice example of something that is

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qualitatively in the right direction. They got a microbiological footprint on about a third of their patients, roughly. And their intracriteria were, over 18, needed to be hospitalized and the keys were new pulmonary infiltrate on chest radiograph within the previous 48 hours and at least two of the following. Cough, purulent sputum or change in sputum, rales or pulmonary consolidation, dyspnea or tachypnea, fever or hypothermia, elevated white cell count, and they had something about the change in the differential, or hypoxia.

So you know, those are, I mean, that is an example. And you know, some of this is about the, you have got to be careful about trying to be too precise on this. When a sponsor comes in with an application, they should have a discussion based on the available data about how you would define it. But this is not a bad map because it got a group A where about a third of the things were

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bacterial and very importantly, you were able to measure a difference between two drugs where one of them should not have worked. And it all went in the right direction. So it actually suggests that it is a rule that collects a bunch of people that have a disease that responds or doesn't to a correct anti-bacterial agent.

ACTING CHAIR TOWNSEND: Dr. Temple?

DR. TEMPLE: Are you also suggesting that you sort of get to test your system by looking at what the fraction of people you do grow a bug in is? I mean I think you are.

DR. REX: Yes, I think that makes sense.

DR. TEMPLE: It has some practical applicability. I mean, if you do all those things, you enter people and you grow something in five percent, you probably ought to revise your standards.

DR. REX: Yes, you have done

something wrong or else you have lost the specimens on the way to the lab. And in either case, that is poor trial execution.

DR. TEMPLE: Yes, so that does become something one could put in the guidance on how to know whether your trial is getting the right people.

DR. REX: It would seem --

DR. TEMPLE: And that is different from being sure that everybody has an organism, which I take your point --

DR. REX: That is correct. It is about saying that the overall syndrome we have pursued is characteristic based on everything we know of a disease that more often than not responds to an antibacterial.

DR. MUSHER: Well then for example, some fraction, like it had one-third of patients have a proven bacterial etiology.

DR. FOLLMANN: I may be reading the study incorrectly, but it looks like close to 90 percent of patients have positive

respiratory cultures.

DR. REX: There were -- well I will try to do the math real quick. They enrolled -- ITT population had 743, let's call it 750 patients. And then if I go to the top of, if I go to table three, they have got an organism out of 132 plus 116. That's about 250. So that is about a third. Excuse my rounding errors.

ACTING CHAIR TOWNSEND: In the interest of moving on, because we have a busy docket ahead of us, any other ideas about how to assess the severity of patients for potential enrollment in a trial for moderate to severe pneumonia?

Dr. Patterson?

DR. PATTERSON: Well, I think the PSI score does need some modification in that mechanical ventilation and pressers should be criteria for severe. I am a little concerned about saying ICU versus non-ICU because I think that can vary from hospital to hospital.

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But in most hospitals, you know, pressers and mechanical ventilation gets you into the ICU. But you can get into the ICU in some hospitals without that. So I think that probably making that more specific.

And then I don't think that the PORT scores have been used at all in pediatrics and that whole thing needs definition.

ACTING CHAIR TOWNSEND: Dr. Wiedermann.

DR. WIEDERMANN: I hope we are not talking about anything for pediatrics here.

ACTING CHAIR TOWNSEND: Any other comments?

All right. We'll go on to 1(b). "Should a microbiological diagnosis be necessary for inclusion in the primary analysis population for the trial and if so, what organisms should be included? For example, pneumococcus or other microbes." And I will throw this out to the panel. Dr.

Calhoun? We are commenting.

DR. CALHOUN: So many people have commented on this and I guess my view is no. I think this is a syndromic disease. And so the inclusion criteria should be syndromic, as opposed to microbiologic.

There is another aspect here that is somewhat compelling to me and that is that the infectious disease society and the ATS and the ACCP, organizations which actually have no agenda, there is no regulatory agenda, there is no commercial agenda, there is no agenda, they are trying to do the best they can for patients, believe also that this is a syndromic disease and microbiologic criteria are not necessary to study the disease effectively.

ACTING CHAIR TOWNSEND: Dr. Patterson.

DR. PATTERSON: I think that it should be sought vigorously but not required.

And with regard to the question

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about what organism should be included besides strep pneumo, the usual things, moraxella, H-blue, mycoplasma, legionella, chlamydophila pneumoniae and MRSA, which has become increasingly common. And I think that in terms of aggressively seeking microbiologic diagnosis cultures, rapid diagnostics, serology should be used.

Regarding viral diagnostics, it should be sent for influenza but also things like adenovirus, which is increasingly common and which is more likely to look more lobar, like a bacterial pneumonia. And we talked, it was mentioned earlier about excluding patients who had influenza.

There are patients with post-influenza bacterial pneumonia, however, and this is being increasingly seen even in young adults and children with MRSA. And they may have and some studies have shown that some of these patients who clearly have MRSA pneumonia with bacteremia and so forth may have positive

influenza titers.

So I don't think that those patients should necessarily be excluded.

ACTING CHAIR TOWNSEND: Dr. Musher?

DR. MUSHER: Just to amplify that. Exactly right. There are bacterial superinfections on top of viral infections. That is the way many of them have been described. So if you isolate a virus, isolate an influenza virus by a rapid test but you also isolate a bacterium, then you would include the patient. But if all you isolate is a virus, you probably shouldn't. At least in your -- the question is how are you going to do your analysis?

And the question was asked earlier, are you only going to include the patients with a proven bacterial infection? And I think what you have got to do is you have got to say at the beginning, you are going to analyze everyone that you put in and you are going to do a subanalysis of the patients with

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a proven bacterial cause.

I also want to comment on Dr. Calhoun's point. It is absolutely true that there was a tendency on that Infectious Disease Society ATS Committee to go toward a syndromic approach. But you have got to realize that several of us on that Committee very, very strongly opposed that. And I just give one simple example. We opposed it because we said guys, here comes methicillin-resistant staph aureus and you are not paying attention to it. And you can't find something that covers everything. And they still went ahead kind of the way they did and we are now faced with MRSA pneumonia and it is not covered by the guidelines.

ACTING CHAIR TOWNSEND: Thank you. Dr. Fleming?

DR. FLEMING: I would concur that it shouldn't be a requirement but microbiological diagnosis should be obtained in as many patients as is practically

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possible. And it takes on some added significance in a trial that is looking at non-inferiority for mortality where you would want to be able to classify which of the patients are consistent with lobar pneumonia, where you could at least do a sensitivity analysis for that group against the other group.

But in general, even in other contexts, I think it is useful to have that assessment in as many patients as possible. And actually, I think FDA also uses that in instances to label, to provide more specifics in the label. So I would encourage it to be done in a substantial, to be achieved in a substantial fraction of patients.

ACTING CHAIR TOWNSEND: Yes, not to belabor the point, I would agree with Dr. Fleming. I would feel that it would be not essential but certainly it would be very helpful to have that information.

Dr. Temple?

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DR. TEMPLE: I thought there was some discussion of this in 1(a) and that the idea was you would try to find a population that was fairly likely to be able to grow something and you would be looking and you would be testing your entry criteria as to whether they were right by discovering that a reasonable number of them had a bacterial origin but you'd count everybody.

But if somebody found a five percent rate of microorganism growth, you would wonder about the trial, maybe.

ACTING CHAIR TOWNSEND: Dr. Wong-Beringer, did you have --

DR. WONG-BERINGER: Yes, I just want to reaffirm, I think, what everybody has said so far in terms of microbiologic diagnosis not being required but strongly sought after because I think the treatment effect may differ, depending on your organism that you are looking at. So therefore, you need to have that analysis.

But I think also, too, that I would like to propose that the FDA encourage the manufacturers to include rapid diagnostic testing in this trial, whether it already has been a standard or not recognized, that they incorporate those studies because that, by relying on this archaic method of culturing organisms on a plate isn't the best way to diagnose or identify the etiology. And I think we need to move the field forward in that.

ACTING CHAIR TOWNSEND: Thank you. I think we will go ahead and go on to C.

"Should strategies be utilized to enrich the population for patients with a particular microbial etiology? For example, pneumococcus or other microbes."

Dr. Musher?

DR. MUSHER: I sort of think, we have already agreed, we are trying to enrich for bacterial infections.

ACTING CHAIR TOWNSEND: All right,

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enough said.

DR. KAUFFMAN: Could I just make a comment that companies probably need to look at where they are going to enlist principal investigators. The people who see these patients first off are ER doctors. They are not ID doctors. Secondly, they are pulmonary doctors and not ID doctors or they are people out in the community in their offices who then would be shuttling them into the ER. So I think really the ER has to be a primary focus and I don't know that it has been in the past. I think if you just go to classic ID physicians, you are going to miss many of these patients.

DR. MUSHER: Just to add to that, especially if you want to avoid patients having had an initial dose of some other antibiotic. Because that is, the official recommendations of the IDSA/ATS are that an effective antibiotic or putatively effective antibiotic begun at the site where the patient

is first seen.

So before the patients get upstairs to the ICU or anywhere else, they have already gotten a dose of an antibiotic in the ER.

ACTING CHAIR TOWNSEND: Dr. Patterson?

DR. PATTERSON: Well, I would just reiterate that not only because of treatment purposes but for matrix purposes and hospitals, anybody suspected of pneumonia in the EC or urgent care, gets a dose of respiratory quinolone very often these days.

And I would just reiterate that the rapid diagnostics, including for strep pneumoniae would be very helpful in analyzing the data and finding these patients.

ACTING CHAIR TOWNSEND: All right. Thank you. Dr. Dowell?

DR. DOWELL: Just to specifically add that testing by multiplex PCR for respiratory viruses should be an expected part of these trials to allow for the subset

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analysis to be done.

ACTING CHAIR TOWNSEND: Thank you. All right, down to 1(d). "Please discuss whether the evidence which shows a treatment effect based on mortality can be linked to endpoints which are used in current non-inferiority CAP trials. For example, clinical success or failure. And if so, how? Note: The possible components of the clinical failure endpoint might include some of the following. Mortality, receiving rescue therapy, lack of resolution of clinical signs and symptoms such that additional antibacterial therapy is administered, a lack of resolution of signs and symptoms at the time the primary endpoint is assessed."

Dr. Fleming.

DR. FLEMING: Well, this is certainly a rich question with many key aspects to it. So let's just take the first literal aspect of the question, can data that shows treatment effect on mortality be linked

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to endpoints that are used, such as clinical success and failure?

So if we wish to do non-inferiority on other measures, can we use the mortality insight and its non-inferiority margin to extrapolate? I think the fundamental principle that first needs to be recognized is that margins that you use are specific to endpoints. You, each different endpoint would have a different set of evidence required to establish that margin. And as we have seen, even with a specific endpoint, the margin will be specific to the patient population. We can justify a much bigger margin in CAP in the more severe patients. But finally, it is specific to the control regimen, as we have understood. We need to justify the margin for that specific control regimen.

Justifying the margin using data for one endpoint to another endpoint is conceivably possible but enormously complicated. The one success story that I can

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think of is in anti-hypertensives that Bob Temple knows extremely well where blood pressure has been a key measure used.

And the question that was raised by Bob and his colleagues to the Cardio-Renal Advisory Committee several years ago is do we now have enough evidence to be able to specifically state by understanding the effect on blood pressure. What is the effect on other measures, such as stroke and cardiovascular death and MI and overall mortality and heart failure and hospitalization? We had 100,000 patients to answer that question.

It is such a complicated question. And it had to be answered across classes. So it was answered in low-dose diuretics and beta blockers and calcium channel blockers and ACE inhibitors and ARBs. And the answer was yes for stroke, maybe for MI and cardiovascular death, overall mortality not so well, and heart failure hospitalization, no. So it is

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a very relevant question. It is a highly data-intensive issue to be able to take on.

Now, what are those other endpoints? The issue is here, the richness of this question is there are other important endpoints other than mortality, absolutely. Determining what they are is an important key step. Before we are asking can we get a non-inferiority margin, we need to be asking, are these the right endpoints? And obviously, this is a complex issue. But the endpoints certainly should reflect what are very important clinically relevant outcomes to patients and the instrument that is used to make that assessment needs to be validated.

So on this issue, I endorse what the IDSA manuscript stated in its conclusions. The IDSA manuscript said, in conclusions regarding what endpoints should be used, what they stated is, in severe CAP, a 15 day all cause mortality outcome measure and in moderate to severe CAP, either a 15 day all

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cause mortality or a composite endpoint that includes morbidity variables that represent meaningful benefits to patients and are assessed with PRO instruments.

And so, with Dr. Musher here who has argued that fever is a key element, they agree. That is in the list. But it is not just fever. It is fever, cough, pain, dyspnea, and fatigue. So that is in fact what is a position that I would exactly endorse, as to beyond mortality in more mild disease, what would be the endpoint measure that we would use? And I also endorse their point that it should be measured with a validated instrument, with a PRO instrument.

So my last comment on this is, business as usual, can we use clinical success and failure?

Dr. Musher said a couple of things yesterday that I thought were really, I think, worth repeating. And one is, it is critical that when you do these assessments, they are

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in blinded trials. These are very subjective endpoints. It is very important. It is also very apparent that if you have very high success rates, assay sensitivity is difficult to validate because the easiest way to make something that is experimental look good when you expect a really high success rate in the control arm, is to be liberal in your interpretation of what success is. And you don't have assay sensitivity.

Well, do we have assay sensitivity with business as usual clinical response, clinical success failure? Well, it was argued that we have an illustration with the daptomycin trial that showed a difference. That difference was 71 percent against 77 percent P value just on the edge of two-sided 05. If you have a completely insensitive measure, you use it 20 times in clinical trials, you are going to see a P value of 05. One time out of 20 by chance alone. That is not telling me remotely that I have assay

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sensitivity with that measure.

So the issues with that measure are, is this a measure that has adequately been defined according to patient defined measures of clinical relevance? And I am okay including fever in there, as long as it is comprehensive looking at these other measures as well, using validated measures that would in fact have assay sensitivity.

So bottom line, the other measures that I would completely endorse would be measures that represent effects on symptoms in mild to moderate disease measured with a validated PRO instrument. And unfortunately, that doesn't lend itself to a non-inferiority margin at this point. But as we develop more insight about use of that measure, that could prospectively be something that could be done.

ACTING CHAIR TOWNSEND: Dr. Follmann, did you have a comment?

DR. FOLLMANN: I just wanted to talk briefly about the idea of using mortality

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data to try and justify the clinical failure endpoint that we have talked about today and has been used in recent studies. And I think Dr. Rex made the point that clinical failure includes mortality as part of it. So how could you not sort of use the old data in some sense to justify a margin using clinical failure.

And I thought about that a little. And I think there is really two perspectives on that. One is if you want to bridge to the past and say if we could have used clinical failure as we currently define it in 1930, what kind of treatment effect would we have shown? And I think we know the answer to that. It would have been dramatic. But it is because the clinical failure would have been driven almost entirely by the mortality.

So if we wanted to imagine what would happen in the past, I think we know the answer. The question for us is really to bridge to the present from the 1930s to now.

And really, we are in a very different situation where the kind of patients we would look at in mild to moderate CAP are not going to have a very high mortality rate.

And so, the clinical failure endpoint is going to be driven not by mortality but by these other resolution of symptoms and other aspects of it. And so it makes it harder, I think, to try and justify bridging from the past into the future using clinical failure.

ACTING CHAIR TOWNSEND: Dr. Venitz.

DR. VENITZ: Can I just respond? I think to some extent I agree with you that most of the clinical success would be driven by mortality but what about rescue medications? Sixty years ago, they didn't have any rescue medications.

So, I do think there are other things that allow you to make that translation. As I said before, I believe that you can translate quantitatively the mortality

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difference that they found 50 plus years ago to clinical success, as we do it today.

ACTING CHAIR TOWNSEND: Dr. Temple.

DR. TEMPLE: I thought people were thinking, from the previous conversation, I thought people were thinking just as Dr. Venitz says, that you were looking for modern death equivalents. That is, you saved somebody's life because you found a rescue medication. Okay, you would have died in the past or, I don't know what else, you put them in a hyperbaric chamber, or whatever you did that would have saved somebody who would have died before, those should still count and because not so many people die anymore.

Some of the other things, cough went on more than ten days, those seem less certain to me, unless that is a current measure of failure. But I must say, it seems very reasonable to take what constitutes failure in the modern world and add that to the mortality, which is what I thought I was

hearing people saying.

ACTING CHAIR TOWNSEND: Dr. Rex?

DR. REX: Thank you. I would like to pick up where Dr. Temple left off. And I have kind of said this before but let me try to say it as succinctly as I can.

Mortality is a powerful endpoint but in the modern era, we work like mad to keep people from dying. They used to die from something as simple and as dumb as an empyema. We now keep them from dying not only from an empyema but from hypotensive sepsis. You know, not always but we sure try hard. And if you are reasonably young, I can probably save you.

So, the mortality benefit that you used to get, well, we are getting most of that now with people who live. And we know that in part because we are not seeing people dying -- the mortality rates have been constant since the introduction of pretty good drugs and we don't see a lot of empyemas hanging around.

So, there is a lot to be said -- we should not be frustrated that when we do a study of pretty sick people -- and actually, I am reminded, Carol Kauffman said one of the entry criteria is or one of the exclusions is always looks like they are about to die in the next 24 hours. I will remind you, every clinical trial has that exclusion in it. It looks like they are about die this afternoon. And for good reason, you don't enroll those people. So, ergo, we really don't enroll the absolute sickest of the sick. Whereas, you know, in 1939, everybody, if they made it to the hospital, they got counted. And they went on to die the next day. So, we are not doing that anymore. So that is another reason why our death rates will not be the 20 percent.

And the danger is this statistical trap that if we have a five percent death rate, plus or minus ten percent, it scares us because it could be as much as 15 percent and we were worried that is a three-fold

difference. That is only if you discount all the biology. So that is theme A. Mortality is a powerful marker but only if you lose sight of the biology and only if you lose sight of the way we are doing clinical trials these days.

The other one is that clinical response is highly relevant. The collection of symptoms that we refer to these days that get you at the end of the observation period to a checkbox yes, did the patient succeed, yes or no, that last checkbox, is a summation, and admittedly there is a physician involved but there is also a patient involved, it is a summation of an extended conversation between the patient and the physician that includes lots of patient reported observations. And the patient has many opportunities along the way to say Doc, I feel terrible. I want out. This drug is making me throw up or I am still having a fever. Lots of ways to get out. There is only one way to get through to the

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end and that is by being pretty clean the entire way.

So, clinical response is what people are looking for these days. We are not going to let them die and so you are going to have to deal with that. And I think you really can map from the old mortality data to a clinical, a comparable clinical benefit.

And we are not asking for this, this is the last theme, we are not asking for this in the absence of anything else. The only thing I did was show you the trial and I didn't tell you anything about why else the drug should work. If I only showed you one trial, you would be correctly skeptical. Dr. Fleming should rake me over the coals if all I show is one bit of data but I don't. I show an enormous wealth of preclinical data. I show that the dose, the exposure at the site should kill the bug. I showed that it worked in other settings. It is a whole stacked up layer of stuff.

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And yes, the daptomycin paper is not about the difference of six percent. It is about the fact that you actually can observe a difference with that tool. That is the minimum possible. And I suggest that you should filter out those who received a prior antibiotic, in which the difference becomes 13 percent, which looks more like the levofloxacin, ceftriaxone, cefuroxime data, which looks even more like Dr. Torno's exposure response stuff. It all lines up because the biology tells you it ought to be true.

ACTING CHAIR TOWNSEND: All right. Dr. Kauffman has a question and then Dr. Fleming has a response.

DR. KAUFFMAN: I was just going to, and not stay it so eloquently, but agree that we really do need to look at patients who don't resolve within whatever period of time they are taken off trial. That means they failed. That is important. And what kind of

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morbidity they are left with at the decided endpoint of the trial. I think that is as important as mortality, which is sort of what John said.

ACTING CHAIR TOWNSEND: Dr. Fleming?

DR. FLEMING: Well, just to follow up on a couple of Dr. Rex's comments. I think what Dr. Follmann was pointing out still is I don't think addressed by what you were saying. My understanding is he was noting that when mortality has substantially changed, then that does alter the comparability of the setting in which you would be looking at those other symptom endpoints compared to now.

Second point, you've again reiterated we don't let people die. And obviously, we do everything we can to prevent people from dying but how do we respond to the Wunderink slide number 22 that says mortality essentially is the same as it was 50 years ago? It has not gone away and we still hear

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that it is the sixth leading cause of mortality. So, mortality remains a significant issue.

Next point, basic science is very important in hypothesis generating and does establish plausibility of benefit but not all agents are the same. And we heard yesterday from Dr. Talbot that there are a number of agents out there that are in fact in trouble, some of which for safety issues, some of which for lesser efficacy issues.

And finally, the daptomycin example alone doesn't validate that we have an ability to make a discernment when you look at the totality of the use of that measure and recognize that, even if the measure is completely insensitive to discern between interventions, even if it were just based on a random coin flip where you had 80 percent chance to succeed, you are going to see a difference of 0.05 in one out of 20 of these experiments. So, it is not a sensitive way to

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validate this as assay sensitivity.

ACTING CHAIR TOWNSEND: Dr. Musher.

DR. MUSHER: So, first of all, I think we are losing track of the fact that we are supposed to be distinguishing between outcome in mild pneumonia where there is no mortality or not enough to speak of and disease of moderate severity or severe disease.

Secondly, I have advocated that we look at the rapidity of the response based on certain clinical criteria. And those clinical criteria are those that what we call as physicians signs, as well as symptoms. And the signs that you would use to evaluate the rapidity of the response include the decline of the temperature from a febrile level to a normal, the return of the respiratory rate, and the return of the pulse to a normal level. And that goes along with, it is hand-in-hand with the patient's interpretation, with the patient's symptoms, and they should all be

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used together.

The fact that there is no difference overall, Dr. Fleming in the mortality, does not tell us that it is the same kind of a disease. I am not exactly sure how to interpret it but I do have to point out that we have far more patients with underlying conditions and co-morbidities. It is very different now from it was in the 1930s, which is what I keep saying. It is so difficult to interpret the data, I am not sure we are doing anybody a favor by dealing with it.

And I do want to comment, finally, on the daptomycin. That is not just a five percent chance there could be a chance because if you did 20 studies you are going to find one five percent off. If I understand Dr. Rex correctly, and even if I don't, I would again add that the failure in the daptomycin group, it wasn't just that the P level happened to make it just around the 0.05, but it the fact that in vitro, the organism, the drug looked

good against the organism.

But once you realize that there is some physiologic effect of pulmonary surfactants, then it becomes a hypothesis. And all of a sudden your hypothesis shifts and instead of saying daptomycin is just as good as some other drug in treating pneumococcal pneumonia, you will say I have got to modify my hypothesis based on additional information that I have.

And when an observation confirms a hypothesis, then it is very different from it is just a random finding. And that was the point several speakers, including speakers from the audience made, when they talked about using the Bayes' approach, what is your pre-test probability.

ACTING CHAIR TOWNSEND: Dr. Patterson had a comment. I just want to remind members, we have got a lot to talk about this afternoon, so we will try to wrap this up real quickly.

Well, I was just going to say I agree with Dr. Fleming in the IDSA position paper about the 15 day mortality and clinical morbidity endpoints to be used. I also agree with excluding pre-morbid patients and that the composite endpoints are especially important for less severe patients. And I also agree that fever shouldn't be the only clinical morbidity endpoint. I think it should be one of them but to include things that white count, oxygenation, malaise, duration of mechanical ventilation. I have a concern about duration of hospital admission because I think that can be, again, based on access to care. And cough, I think, should be included, although with mycoplasma, in particular there can be a persistent cough due to bronco spasm. So that again, these need to be looked at as a composite.

ACTING CHAIR TOWNSEND: Dr. Fleming, did you have a comment?

DR. FLEMING: Well, I think, Dr.

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Musher, you and I are agreeing again. Maybe sometimes we say things somewhat differently but you were saying that mortality is a result now of very significant complexities in how this disease process has evolved.

All I am saying is the reality is mortality is still part of what we confront here. Mortality hasn't gone away and it is not a setting where we can say this is no longer an issue we can just deal with other components.

DR. MUSHER: Of course.

DR. FLEMING: Those other components are important but mortality is certainly one remaining aspect that is still with us in a significant way.

ACTING CHAIR TOWNSEND: One last comment by Dr. Venitz, then we will move on to the next one.

DR. VENITZ: Yes, as the token clinical pharmacologist, I wanted to add something and I think this is probably the

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most appropriate item to add and that is the idea of exposure response. I mean, really, what this item D deals with is do we have proof of efficacy, effectiveness? And one way of supporting at least the proof of efficacy would be to show that internally you have some dose response, or in this case, concentration effect relationship that is consistent with their prior expectations. And we saw a nice example yesterday. There were several examples on some of the slides.

So I would reiterate the recommendation that was made yesterday to include PK samplings so we can actually look at AUC or MIC ratios and use that to support the proof of efficacy. I realize it is not randomized but it is part of a clinical trial and it can provide supportive evidence.

ACTING CHAIR TOWNSEND: Thank you.

All right, we will move on. "1(e). The historical evidence for a treatment effect is based on studies which evaluated

penicillin, sulfonamides, and tetracyclines. Given the need to preserve the treatment effect, the effect of the comparator agent, or the placebo, or no treatment in a future study, what are appropriate choices for comparator agents? Please explain the basis and information that supports the recommendation for comparator agents for a future study."

Dr. Musher.

DR. MUSHER: I think appropriate choices should be medications in accord with official guidelines. And unless anybody objects, I think we should go on to the next question.

(Laughter.)

ACTING CHAIR TOWNSEND: Dr. Temple.

DR. TEMPLE: I just wanted to mention, it is okay if the thing you use is better than the thing in the past. That doesn't undermine the design or interpretation of the study at all. So that is always okay.

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ACTING CHAIR TOWNSEND: I would agree with Dr. Musher. Dr. Patterson.

DR. PATTERSON: Yes, I agree and I think that is pretty straight forward. The only comment I had related to that is, Dr. Musher has already pointed out, that those guidelines don't cover MRSA. So, because it has become so much more common if the drug to be studied is anti-MRSA drug, then the comparator needs to have MRSA included as well, inspector.

DR. MUSHER: I, of course, agree with that.

ACTING CHAIR TOWNSEND: Dr. Fleming.

DR. FLEMING: Relative to a non-inferiority trial on mortality, certainly what would be preferable is to use an agent that would be confidently maintaining or improving upon the effects of the sulfonamides and penicillin. And we don't have to stick with those agents but we do need evidence to

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indicate through meta-analyses which do exist that other classes of agents that are now more frequently used are in fact at least maintaining the efficacy of those historical agents.

I would, though, urge that the best care possible be taken to choose what consensus is today as the best agent for an active comparator. Bud, I thought, got at the issue that concerns me here already in an earlier comment that he made. We talk about the risk of non-inferiority trials, not having assay sensitivity, potentially allowing us to not maintain the efficacy of current available therapies. Current available therapies are highly effective. We can't walk away from that efficacy.

If we do non-inferiority trials, the margin as it is set up, particularly if you are not as rigorous as what we were talking about, can allow you to be estimating the new agent to be worse than the active

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comparator and still satisfy the non-inferiority margin, which is one of the reasons you want a tight margin to at least make it likely that success is something that is similarly effective. But you could have, in fact, an estimate of somewhat less effect and still get approved.

The concern that arise, and Bud eluded to it, is you do two or three generations of these non-inferiority trials and now you could start meaningfully erode. And that is called biocreep. And so I would urge that a lot of attention be given, just as we said exactly appropriately earlier on, it is inappropriate to do a superiority trial against a lame duck active comparator that is at least giving people something, but giving them something weak so that we can beat it. That is not ethical. It is not scientific.

We need to give people the very best thing we can on the active control arm. And if we do that, if we select the best that

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we believe for antibiotics as the active comparator arm, it is what is most ethical and it provides some protection against biocreep if we then have generations of non-inferiority trials on non-inferiority trials.

ACTING CHAIR TOWNSEND: Thank you. Dr. Rex.

DR. REX: Dr. Fleming, as always, raises very good points. And let me say a couple of things that might be helpful here. And keep in mind I used to be an academic physician. So I am going to say a couple of things about how one might view industry.

You can say to yourself, gee the guys and gals in the industry are trying to find the simplest of the, they are trying to find the work-around, they are trying to slither through with something that isn't quite right. You can think that but in fact if I am going to spend forty million dollars doing a pair of CAP studies, I would be a fool to study my drug against a crummy comparator

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because, when I am done with those trials, I have to show them to the likes of you. And if I studied my drug against, I don't know, an under-dosed regimen with Pen-Vee K and I come in and I say, Dr. Kauffman, I beat Pen-Vee K. She'll say, John, what are you doing. And as well she should.

I actually want to choose, I am motivated to choose, a good solid modern comparator so that when I take my data to your Pharmacy and Therapeutics Committee, I can say, look, I did as well as name of good drug. And everybody will recognize that that is a good, current, modern drug and that my study is good.

So it is not like it is a legal check and balance, but there is a commercial medical check and balance here that you should be aware of. We are going to choose a good regimen because that is what the payers want. That is what is going to be compelling. So do keep that in mind.

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And the biocreep thing, I think, is clearly a theoretical possibility. In the case of modern antimicrobials, where we have got all this preclinical stuff, including the current concepts around mutation and prevention concentrations, you may not be aware of this, but we now understand a little bit about the shape of the exposure curve that permits mutations to occur, mutations to resistance. And we actually would like to dose above that, even if we could.

So, we are working really hard to give adequate exposures because again, that is in my best interests as a sponsor. It means my drug will be last. My drug will be convincing. Resistance won't develop. So, it is another one of these checks and balances that isn't immediately obvious. But when you start to design clinical programs, you begin as a sponsor to say, you know, I want this to be compelling. I want this to. So, I want a hard test because if I do well on that test,

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everybody will say yes, I want to use that. That is what makes a really special drug.

So, the biocreep thing is a concern but I think it is more theoretical than it is actual because you are not going to come forward anymore with an inadequate dosing regimen based on pharmacodynamics. It used to be, before we understood all this 20 years ago, you might kind of wander around in space. But these days, you don't do that very much.

And finally, the last thing I would like to say has to do with this what it means to hit minus ten percent on a margin. Dr. Fleming eluded this but let me try to say it in my simple, my way because I try to carry around a little sort of benchmark points. And the benchmark that I carry around in my head goes like this: If you are thinking about a therapy that works 90 percent of the time, roughly, and you do a study of 250 patients per arm, so a 500 person study, a reasonable science study, 250 per arm, the target

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activity of the control is around 90 percent. If my new drug is going to have a margin no worse than ten percent, my new drug is no worse than ten percent, then if the old drug hit 90 percent dead-on, then my new drug, the worst it can be and satisfy that criteria, is 87 percent. It can only be three percent away because the 95 percent CI will be, I am rounding, three plus or minus six. And that will take me from like minus nine to plus three, roughly. Give me a half a percent or a percent either way.

So, it is really helpful to realize that 250 per arm, target is 90 percent, I can only be three percentage points away and still be non-inferior in terms of my point estimate. I have got to actually, and Tom said it very well, they have got to almost lay on top of each other. Very close. That is the worst I can be. So when you talk about a minus ten percent margin, it may sound like a bunch but when you work the numbers, I have actually got

to be quite close.

So, I think that is a helpful thing to recognize, so those three ideas. I want to choose a good comparator, it needs to be modern, I want it to be well-dosed, and the rules we are talking about are really stronger than you might think. Sit down and work with the numbers. They are pretty good rules.

ACTING CHAIR TOWNSEND: Thank you. We'll go ahead and move on to the last question in number one. "What is your best estimate of the treatment effect size (M1) that the historical data support for treatment of hospitalized CAP (based on severity selected in part A of this question, so meaning moderate to severe) in a future CAP trial? And what is your recommendation for a non-inferiority margin that preserves a proportion of the treatment effect, that is, M2, for a CAP trial in this population with the endpoints discussed above?"

Dr. Dowell.

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DR. DOWELL: Twenty percent and ten percent.

ACTING CHAIR TOWNSEND: Easy enough. Dr. Calhoun.

DR. CALHOUN: I am still somewhat compelled by the proportional reduction in risk that we have seen across all severity. And so, although I don't disagree with the absolute numbers that have been suggested around the table by the IDSA, etcetera, I think that the proportional hazard model has some value.

ACTING CHAIR TOWNSEND: Dr. Whitney?

DR. WHITNEY: I find this discussion of margin a little bit tricky because I feel like we are sort of trapped by what is feasible. In an ideal world, we would like to have that M2 be as small as possible but yet we don't want to discourage the development of drugs. And we haven't really had, I mean, we have thrown around some sample

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sizes but haven't really seen a table of how it really affects it to discuss different margins.

So, I mean, is ten percent the smallest we can really do? And if that is the case and still get good drugs, maybe that is the choice we have in front of us.

ACTING CHAIR TOWNSEND: As Dr. Rex pointed out with that ten percent margin, we are really talking about a three percent difference. There is probably not that much difference in a ten percent margin, in a five percent margin. Is that right?

DR. REX: Well, that is always dangerous to talk statistics in front of a real statistician. You understand that I am not.

The quirky thing about the margin is that there is a calculation has, it is the square of the margin in the denominator. So there is this numerator up here, I won't tell you how you get that but pretend there is a

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number up here, and as you shrink the margin, you are dividing by the square of it, and so it gets smaller pretty -- You're going from ten percent, which would be ten times ten is a hundred, divide by a hundred, as opposed to five percent. Five times five is twenty-five. You have actually gone up four-fold in terms of your sample size going from ten percent to five percent, more or less. Have I got it right? Is it set up, I'm doing okay?

DR. FLEMING: You have it right.

DR. REX: Okay, so good. Thank you. So that is dramatic. That is a shift. You know, I told you my little mental benchmark, 250 per arm, 500 patient trial and 90 percent. If I now want it to drop down to a five percent margin, I am now talking two thousand patients.

Now, my overall trial program might have two or three thousand patients in it and actually it will probably need to, so that I get some safety, you know, I get a bunch of

other stuff with that. But to dedicate two thousand patients to one trial and then Dr. Temple says, John, where is your second trial, I go, oh, no, I forgot about the second trial. It would be hard.

So, you are right. To some extent, we are talking about the bounds of the feasible. That is the bad news. The good news is, when you add up what we know, thankfully, we have got information to suggest that we are actually, we are working with some clear blue space here between the mortality effects that we know that turn into morbidity effects in the modern era, they are pretty striking. So, we have got a little bit of room, a ten percent margin, as Dr. Townsend said, I have got to come pretty close to hit that ten percent. So, it is not as bad as you think. You are not letting us off that light.

ACTING CHAIR TOWNSEND: Dr. Temple?

DR. TEMPLE: Yes, it is always worth remembering it is so important to us

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that it not be worse than the margin that we put very high statistical assurance on it. You know, that is the lower bound of the -- upper bound of a 95 percent confidence interval. That is not the best guess about what the real difference is by a long shot, which is much closer to the point estimate or something else.

So, it is chosen conservatively, just the way we use a P of 0.05 but the value that you exclude with a P of 0.05 in a superiority trial isn't the best estimate of the effect. Nobody would every use a drug that was significant to 0.05 because it would be just a hare's breath better than nothing.

So, we simultaneously do that to be cautious but also take into account the actual effect side. So that is just what everybody has been saying.

ACTING CHAIR TOWNSEND: Dr. Whitney, did you have another comment to make? And then Dr. Fleming.

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DR. WHITNEY: Oh, just a follow-up on the size of the margin. I think, given our discussion, I am pretty comfortable with the ten percent margin and then, adjusting for the relative risk. But then are there some endpoints where it needs to be larger for some feasibility or can we use that across the board for the endpoints?

ACTING CHAIR TOWNSEND: Dr. Fleming?

DR. FLEMING: Well, I was going to get to your first question. But to start with your second I'll come back to what I had said a couple of minutes ago.

The answer isn't what is the margin we use in CAP because the margin is very specific to the endpoint that we use and the scientific data that we have regarding what is the effect of an intervention on that endpoint. So, then it is therefore also specific to the active comparator that you are using and, as we have seen, it is specific to

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the patient population.

So the ten percent margin that I have supported in the mortality setting is in the context where you have patients that have a 15 percent or higher mortality on the control, but we can use the relative risk to extend it to lower levels. But it is very specific to the intervention, the endpoint, and the patient population. We can't just generalize margins.

But to come back to what Dr. Rex was pointing out, he does have it right if you said, let's say to use your specific example, you had a 90 percent success rate on the control and the intervention, let's say you are using a ten percent margin, which would be already a very generous margin, if you had a 90 percent success rate, but to go with your point, you would succeed if you had three percent absolute increase. Which is, though, a one-third increase in failure. But if you go to a 15 to 20 percent margin, now you could

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succeed, even when you are doubling the failure rate.

And so, it is very tempting to make that margin bigger because, your intuition is exactly right and Dr. Rex is exactly right about his formulas, you double that margin. You cut the sample size by a factor of four doing two things. A, making it a whole lot easier to complete the trial in a timely way and cutting resources and B, making it a whole lot more likely to be successful. Well, we want to be successful, except in those settings where you don't actually have an agent that is the same or even comparably effective. And you set that margin at 15 or 20 percent and follow Dr. Rex's correct logic, you are now going to declare success when you have doubled the failure rate. Now, all bets are off on biocreep because you are, in fact, putting people at significant risk in the future of A, being treated with substandard interventions but B, with a couple generations

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of this losing the important gains that we have achieved through effective antibiotics.

ACTING CHAIR TOWNSEND: Dr. Rex.

DR. REX: I don't want to hog the microphone but philosophically, there is a difference between P values or 95 confidence intervals and truth. There is because P values -- I didn't mean to elicit humor with that. P values were invented many many moons ago as a way to help us decide. We had a hypothesis and we did an experiment and we get some data. Do the data support the hypothesis? That is what P values are about. They are a way to help us mechanically decide that. But that is only about that one experiment. I have said this many times but it is just fundamental. You don't do the experiment in isolation. And indeed, you can take the same set of experimental results with different mental road maps and get different P values from it. And there is marvelous pair of articles from 1999, a fellow named

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Goodman in the American Journal of Medicine, I believe, where he demonstrates this. The first one is called "The P Value Fallacy" and the second one is about the Bayesian modification of that.

But the heart of it is that P values are a tool to help us think critically about our data but they are not the truth. The truth comes from -- how do you get the cosmic truth? You can't get the cosmic truth but you can say, I started my experiment knowing a lot of things ought to be true and now I have done an experiment that either did or did not line up. How much does that experiment change my believe model?

In the case of antimicrobials, unlike let's say the case of a novel mechanism cancer agent, where the hypothesis is if I interfere with mutant K-ras expression, I am going to alter the course of non-small cell lung cancer. That is a very complicated hypothesis for which I have got relatively

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little prior data.

On the other hand, if I talk about an active agent that killed it in the test tube, cured the mouse, got the right exposure, figured out the exposure, Ambrose and Drusano helped me figure out what the exposure is that keeps mutations to resistance from occurring. I delivered that exposure into the lung. It would surprise me if I didn't cure some pneumonias. Now, it could happen and that is why I do the experiment but it would surprise me. So I start off with lots of reasons to believe it is true.

So keep that in mind that if all I showed you was one 250 patient per arm study, if that is all I showed you, every one of Dr. Fleming's criticisms would be true ten times over. It would not be a compelling dataset. But that is not all I shows you. I show you the other experiment, the one I didn't forget to do, the second CAP study. I show you something, you know, maybe something else with

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this drug. And I show you all the mice that I cured. I don't introduce you to them personally but I do show you the data about the mice that I cured along the way.

So, it is, we don't do these in isolation and I think that is very helpful to me as a developer. It is one of the things that we really rely on. We say that with an antimicrobial, once I demonstrate adequate pharmacology at the site of infection, it really has a good chance of being a drug. And short of adverse events, for which I am going to look assiduously, that is why I am going to have several thousand people in my total clinical trial. I am looking for those AEs because the last thing I want to do is let a bad drug out because that will come back and bite me.

So, I am going to do all that work but I start off, after the end of about phase one, feeling really pretty good. You know, I have got a good reason why it ought to work.

And actually, it is more likely to work than not.

ACTING CHAIR TOWNSEND: Thank you. A quick reply from Dr. Fleming.

DR. FLEMING: Just very quick. Agree again with a lot of the spirit of what you are saying. Just one refinement. You are saying our prior belief here, when we have gone through all that preclinical and other work is that it is more likely this agent is effective than what you might have with a novel anti-cancer agent you are saying. I can accept that probably is true.

What we are talking about though is the null hypothesis here, is that is relates to the effect against what you have already agreed that we would automatically do, take our best choice antibiotic out there, our best choice antibiotic out there and we are going to go head to head with that. And we have ATS IDSA guidelines. Those guidelines don't say use whatever you want. Those guidelines are

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basically saying there is a totality of evidence here that say we actually think there could be differences in certain settings and we are going to take the best one. And now you are telling me your preclinical data tell me in advance that I am the same of the best of all choices.

So the prior here, if you want to be a Bayesian, as you are thinking, isn't just is this somewhat effective but your prior is. I'm going head to head because you told me that we would use the best and you assured us we would, that this is comparable to the best of the antibiotics and IDSA and ATS acknowledge that not all antibiotics are the same.

DR. REX: But we test them in the lab. You know, I take the ones that I think I am going to run against. But let me saying something about animal models because I have done an enormous amount of these in my career. They don't map one to one to human beings.

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That is why you end up doing the human experiment as well.

There are little differences -- not little differences. There can be big differences in drug distribution, big differences in protein binding, big differences in tissue distribution. And also mouse pneumonia isn't exactly the same as human pneumonia. So you do need to do the second experiments.

But we do try to work against good drugs. And if I said best earlier, I think it is important that we not put down a standard that says you must use the best comparator regimen because best is really a slippery term. What you want is a well recognized good regimen. There can be a lot of debates on what is best but if the ATS puts it at the top of its list, that ought to be a one that is acceptable.

I have been in debates about what is the best and also what is the best in one

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country may be different from what is judged to be the best in another and there would have to be some consensus but it better be a good one. Because remember my test at the end of the day, I have to walk around to all the hospitals in the world and say here is my dataset and I tested against X. And I am going to want them to say I recognize X. That is a good choice. You have done well. That is the ultimate test. It's not even the people in this room. It is that test. And to satisfy that, I have got to choose a pretty good one.

ACTING CHAIR TOWNSEND: Okay. Thank you. In the interest of moving things along, we are approaching 3:00 here, to answer FDA's question, there are some recommendations that have been made by members of the panel also from the IDSA that for the circumstances that we are discussing, which is moderate to severe pneumonia with a mortality endpoint, that a ten percent margin would be reasonable.

Are there any objections to that? Any comments on that measure? Dr. Rex?

DR. REX: I didn't hear the Committee agree to just mortality. I heard a pretty significant undercurrent for a mortality plus. A combination of pretty strong clinical things and we have seen some examples of studies where that is. But I'm sorry, that is what I thought I heard. And I don't want us to slip into the pure -- excuse me, I should say that the pure mortality endpoint has a little statistical twist about if you don't quite have enough desks because the physicians are doing a really good job keeping the patients alive, it is good for the patients, it is bad for the study.

ACTING CHAIR TOWNSEND: Dr. Patterson.

DR. PATTERSON: Well, I am going to go with the IDSA position paper in Table 5 on page 34, that suggests 10 to 20 percent for composite clinical response.

ACTING CHAIR TOWNSEND: Thank you. Does that answer your question, Dr. Cox? Thank you.

All right, we will move on to question two. Thank you very much for all the discussion.

Again, I will read the question and then I will ask for votes. Dr. Musher, I will start with you. When you give your vote just give your yes because I am asking for yes votes initially. Right. So, I will ask the question. You raise your hand I will call on you. Please give your name and say yes.

DR. FLEMING: Could we make sure we understand the question --

ACTING CHAIR TOWNSEND: I'm going to read it.

DR. FLEMING: -- I mean, as we did before the first one?

ACTING CHAIR TOWNSEND: I'm going to read it and if you don't understand it after I read it, then I will --

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DR. FLEMING: Okay.

ACTING CHAIR TOWNSEND: All right. "Given the information presented mostly from historical data on the treatment effect of drugs for community-acquired pneumonia in patients with pneumococcal/lobar pneumonia, please address the following questions on trials of outpatient community-acquired pneumonia (studies using an oral drug)."

The first question is yes/no. "Can a treatment effect be reliably quantified for a non-inferiority study of outpatient community-acquired pneumonia, that is, for an oral drug?" If your answer to that question is --

DR. MUSHER: My answer to the question is yes. And my further statement is that the first paragraph has nothing to do with my answer.

ACTING CHAIR TOWNSEND: Thank you, Dr. Musher. So, if your answer to that question is yes, please raise your hand.

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Does anybody need clarification?

DR. FLEMING: I do.

ACTING CHAIR TOWNSEND: Okay.

DR. FLEMING: So I do want to make sure I understand the question and I want to understand it in the context of what I thought was a very intriguing concept race yesterday by Dr. Temple. And that is, upon completion of a trial in severe CAP patients, let's say based on a successful achievement of non-inferiority mortality, one might be willing to extrapolate that result to a label in CAP.

DR. MUSHER: That is question three, if I am not mistaken.

DR. FLEMING: It's question three.

DR. MUSHER: See, that's going to come up. I don't mean to interrupt but Mr. Chairman, I think that we are going to deal with that in the next question so that shouldn't enter into the present one.

DR. TEMPLE: This is really about whether you can reach a conclusion just in

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this population, not whether you can extrapolate a conclusion from really sick people --

DR. FLEMING: So, okay --

DR. TEMPLE: -- to less sick people. But could you do a -- this all goes to the oral only drugs. You know, that is --

DR. FLEMING: All right. So, if you are of the perspective that you could generalize a persuasive result from the severe setting to a label in CAP without having to do a separate study, then one shouldn't answer this question yes. You should only answer this question yes if you believe that you have the ability to formulate a non-inferiority margin in limited patients on mortality or on a non-mortality endpoint?

DR. TEMPLE: Yes. But I mean, as everybody has expressed it, there are some drugs that don't have an IV form. You can't necessarily do that first study in them. What are they supposed to do? That is what this is

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about.

DR. FLEMING: But that presumes that you wouldn't ever use an oral therapy in severe disease.

DR. TEMPLE: Well, the idea is mostly you would start IV and then switch. But that is different. Again, this is for where there is only an oral form and the presumption is people who are brought in really sick are probably not going to be started on that. So how can you test their effectiveness in CAP? That is what two is about.

DR. FLEMING: So, if you had quinolone, for example, would you not be willing to have used that quinolone in severe -- in fact, isn't the blood concentration oral and IV in quinolone similar?

DR. TEMPLE: It is seemingly pinning us down when one might find a solution to this problem to be that -- use whatever you want. Use an oral or an IV, whatever you

prefer to use in this severe trial that we are going to do. And if you find it is persuasive, you might be willing to generalize that conclusion to the mild setting.

DR. COX: Yes, I mean, typically just thinking about the patients who are sick, who are coming into the emergency room acutely ill, I mean, I would expect most as part of standard of care would get IV therapy. You know you do raise the issue of comparable levels but in the setting of somebody who may be very sick, IV therapy is probably standard.

DR. FLEMING: But if you use IV therapy there and you are willing to say then just do a bioequivalent study showing that you are achieving appropriate concentrations to switch from IV to oral, if you are willing to say that, then you know --

DR. TEMPLE: No, that gets drug A, which is available in both forms studied. Question three goes to whether your are willing to extrapolate. Now, talk about drug

B. It doesn't come with a parenteral dosage form.

As Ed says, most of the time, most people wouldn't want to start a really sick person off on an oral. I mean, what do I know? That is just what I am told. So, how can you work up a drug like that for CAP in presumably people who are a little less sick. That is what two is about.

DR. VENITZ: All right. But isn't outpatient care using an oral drug substituting basically less severe illness?

DR. TEMPLE: Yes.

DR. VENITZ: Just like IV --

DR. COX: That's right.

DR. VENITZ: -- inpatient was a substitute for more severe illness.

DR. COX: Correct, yes.

ACTING CHAIR TOWNSEND: Dr. Wiedermann.

DR. TEMPLE: So these are less severe. The documentation of success that

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everybody agreed was okay may not apply to those. What is your margin in these?

ACTING CHAIR TOWNSEND: Dr. Wiedermann?

DR. WIEDERMANN: So I would respectfully ask the FDA to change their question to say for mild pneumonia.

DR. PATTERSON: For mild to moderate.

DR. COX: That was the intention. I mean --

DR. PATTERSON: I think mild to moderate.

DR. COX: Yes, we are getting at potentially more mild to moderate pneumonia. The group of folks who would typically get oral drugs in the outpatient setting.

ACTING CHAIR TOWNSEND: Dr. Rex?

DR. REX: I think, if you think in terms of -- you can be reasonably ill and still take something by mouth. And you can even sometimes have somebody in the hospital

who takes something by mouth. You are giving them IV -- you have them in the hospital because you are giving them IV fluids and maybe giving them a little supplemental oxygen but you actually might be comfortable dosing them by mouth because it is clear that their gut is working.

And I think that rather than just, if you use the word mild, you envision somebody who is happy, walkie-talkie, doesn't really need much. And that is not necessarily the case. You can be acutely relatively ill and still be happily treated by mouth.

And I would say, the sponsor group has not extensively discussed this, but it would seem the case that I am, if I am studying my oral only drug and I want to get some reasonably strong outcomes, I am going to be encouraging my investigators to look for people who are reasonably ill but who can take things by mouth. I am going to try to get some older people, for example. Because we

know that older people are at risk of worse outcomes. Yet, I have got an older person who is not terribly ill. You know, they are 70 they are not hideously ill but they are high risk. So, I am going to be looking for -- and that would be a person with a PORT, as we said earlier, PORT 4.

So, I am going to be looking for some people who are like that to get into my oral study because I think that is what I am going to have to do to help make the case. So, don't be distracted by the word mild. Mild doesn't actually cover it entirely.

So, I think it is the idea of I can only study them oral but that is a pretty good spectrum.

ACTING CHAIR TOWNSEND: Dr. Follmann.

DR. FOLLMANN: I wanted a little clarification on the term treatment effect. So that is relative to a placebo, I assume and then there is also would be an issue of what

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endpoint you would have in mind. And my endpoint in mind for this, you know, mild CAP would be clinical failure or something like that, not mortality.

DR. COX: Right, yes. The treatment effect here is effect over placebo. And just like the other question, because all of these issues are interrelated, you know, you kind of have to answer the question about can you define a non-inferiority margin keeping in mind what population you are referring to and what endpoint you would be also thinking of. So those things are all kind of packaged together in the question.

ACTING CHAIR TOWNSEND: Right. In terms of trial design, what we are talking about is mild to moderate pneumonia, being treating as an outpatient with an oral formulation.

DR. TEMPLE: And can you figure out what margin to use? I mean everybody was happy that for the sicker people, we got an

idea of what the margin is. Can you do the same thing here?

And you know, I thought some of the concentration response stuff was interesting but is early. And that is the question.

ACTING CHAIR TOWNSEND: Okay. So, is everybody clear on the question?

All right. So again, given those criteria, can a treatment effect be reliably quantified for a non-inferiority study of outpatient community-acquired pneumonia, that is with an oral drug and presuming this is mild to moderate pneumonia?

So, if I could see a show of hands if your answer is yes.

(Show of hands.)

ACTING CHAIR TOWNSEND: All right. We can start with Dr. Wong-Beringer.

DR. WONG-BERINGER: Annie Wong-Beringer, yes.

MR. MAKOWKA: Ken Makowka, yes.

ACTING CHAIR TOWNSEND: Dr. Musher.

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Dr. Dowell --

DR. DOWELL: Passing.

ACTING CHAIR TOWNSEND: Passing, okay. If you can keep your hand up so that we know that you are a yes.

DR. MUSHER: Okay, Daniel Musher. I am voting yes.

DR. PATTERSON: Jan Patterson, yes.

DR. VENITZ: Jurgen Venitz, yes.

DR. CALHOUN: Bill Calhoun, yes.

DR. KAUFFMAN: Carol Kauffman, yes.

ACTING CHAIR TOWNSEND: Greg Townsend, yes.

DR. WIEDERMANN: Bud Wiedermann, yes, to be qualified in a moment.

ACTING CHAIR TOWNSEND: Okay.

DR. WHITNEY: Cindy Whitney, yes.

ACTING CHAIR TOWNSEND: Okay, thank you. So, now the nos?

Dr. Dowell, you can speak in the microphone, say your name, say no.

DR. DOWELL: I really wanted to say

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yes but --

ACTING CHAIR TOWNSEND: You are allowed.

DR. DOWELL: -- to be honest.

ACTING CHAIR TOWNSEND: And you can change your vote later.

DR. DOWELL: I think in the Senate, aren't they allowed to do not present or what is that thing? Are we allowed something like that? Abstain?

ACTING CHAIR TOWNSEND: You are allowed to abstain.

DR. DOWELL: My problem with voting yes is then you get to these next questions which stump me. How would I justify that?

I guess, if I understand this right, we are going back to the studies in the early 1960's, the military studies of outpatient military people with mycoplasma. And we are asked to use those studies to answer these three subsequent questions and I am really just getting stumped by that. So,

I guess I am -- so that is what I mean by no.

ACTING CHAIR TOWNSEND: Okay, no. Dr. Fleming?

DR. FLEMING: Tom Fleming, no.

DR. FOLLMANN: Dean Follmann, no.

ACTING CHAIR TOWNSEND: Okay, we've got everybody. Dr. Musher, if you wouldn't mind starting off?

DR. MUSHER: Well, my vote yes did state that I thought it had nothing to do with historical data. I would amplify that by saying I don't think there are historical data for pneumococcal disease. I know for a fact there are no historical data for Heamophilus or Moraxella disease. That covers your -- and I know for a fact there is no data on staph aureus because I have written on that one, too. I know the literature very well. So, that covers the bacteria.

Mycoplasma is a totally different kind of infection and I have got no problem with that but I do have to say that we talk

about enriching our study for bacterial disease, we have really -- to have that discussion in the case of mild pneumonia, are we in fact trying to enrich for bacterial disease or are we not enriching for bacterial disease? Because the response of mycoplasma is going to be pretty different. It has already been pointed out nobody is going to die of it and you can keep coughing for weeks and weeks and weeks. So, it is a little difficult to say what you are going to look at.

And I will comment on the individual questions, as they come along.

ACTING CHAIR TOWNSEND: Okay. Dr. Patterson.

DR. PATTERSON: Well, I said yes because I think some of the patients that we used to treat inpatient we are treating outpatient now, due to better formulations. And I think it is a study that needs to be done and there is a way to do it with looking

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at clinical morbidity indicators.

DR. VENITZ: I voted yes because I think there is some evidence in the literature to suggest that mortality is impacted at least 60, 70 years ago. The second driver of my vote was the fact that I don't think it is ethical to do a placebo controlled trial. So, you are stuck.

ACTING CHAIR TOWNSEND: Dr. Calhoun?

DR. CALHOUN: So, my yes vote, the qualification on that is that in segue from Dr. Venitz's comment. I think the proportional hazard reduction looks strong to me. The absolute numbers do not look strong to me. So, I think the effect is a reduction in proportional hazard in the milder patients.

And likewise, I think doing these studies in any other way, that is in a placebo controlled fashion, is really not an option. So, if these studies need to be done as I think they do, we need to find a way of

conducting them.

ACTING CHAIR TOWNSEND: Dr. Kauffman.

DR. KAUFFMAN: I voted yes because I think this is a population that needs to be studied. And the drugs that would be brought to bear are probably going to be important drugs in our armamentarium as time goes on. I think we can enroll patients, again, starting maybe with the PSI criteria of two to three.

And I think doing these trials means you are going to have to follow them very very carefully. Much more than you normally do with an outpatient kind of study. So it is going to be fussy. But I think with that you can get data day by day, just to see the progression of the disease and how the patient gets better. Then you will be able to follow those clinical criteria for endpoints because I don't think mortality is going to be one of your endpoints.

ACTING CHAIR TOWNSEND: I voted yes with some trepidation. But I feel like there is enough historical data to suggest that there is a treatment effect in this population. I think there is some data on what that treatment effect is and that this is a population that needs to be studied.

DR. WIEDERMANN: And my qualified yes, I think, was very similar to Dr. Dowell's no. I think there seems to be enough evidence out there for mycoplasma disease. But I would be hard-pressed to choose an M1 for this study population for bacterial pneumonia.

ACTING CHAIR TOWNSEND: Is that it?

DR. COX: Was that a no, Dr. Fleming?

ACTING CHAIR TOWNSEND: Dr. Fleming said no, I believe. Dr. Whitney.

DR. WHITNEY: I voted yes. I think I agree mostly with what Jan said. I think a lot of these patients that are now treated as outpatients would die if they were left

untreated like they used to be.

So, I think the patients aren't so different. It is just that we are catching them earlier. We are treating them. I do think we have to use something else as an endpoint, obviously. But we need oral agents and we should come up with something.

EXECUTIVE SECRETARY MOSADDEGH: For the record, it is three nos, ten yeses and one industry representative no vote. Thank you.

ACTING CHAIR TOWNSEND: Dr. Wong-Beringer?

DR. WONG-BERINGER: I voted yes because I think again, this population effected, it is large. Not only those who have mild disease but those who transition from severe disease to mild to moderate after receiving IV therapy. So, we need an oral drug and we need a way to look at the effectiveness of antibiotics out there. I think it does need to be, in this setting, compared in a blinded trial for patients

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looking at the treatment effect not on mortality, per se, but on composite endpoint built on morbidities that had been discussed before. And that it is also important to look at the time to respond in this setting, as opposed to the end of treatment only.

ACTING CHAIR TOWNSEND: Dr. Makowka?

MR. MAKOWKA: I am not a doctor. I agree because it has to be done. We have to see the efficacy of this in the milder patients to possibly prevent it to get to the more severe patient.

ACTING CHAIR TOWNSEND: We ask the nos to explain their no votes.

DR. DOWELL: What I said before. I have nothing more to add.

DR. MUSHER: I also have nothing more to add.

ACTING CHAIR TOWNSEND: Dr. Musher, you were a yes vote. Is that correct?

DR. MUSHER: I was a yes vote.

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ACTING CHAIR TOWNSEND: Okay, I just wanted to make sure.

DR. MUSHER: I was a yes vote and I have already made my comment and my reservation about that first paragraph of that wasn't relevant. And my right to make comments on the individual Roman numerals that follow.

DR. FLEMING: So, in responding to this, if we were using a mortality endpoint, it is, I voted no, but I could conceivably vote yes, although I think the plausibility that somebody would be doing a mortality endpoint trial in mild disease is very low. And it is also quite an extrapolation, even if we use the relative risk of 1.67.

But if this were viewed as mild to moderate and somehow it was viewed to be plausible that we could achieve enough events, enough deaths in order to be able to assess a mortality endpoint, then it is possible that one could justify a margin for that endpoint.

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I voted not because I presume what people were really more thinking about was a symptom-based measure. And again, I endorse what is in the summary conclusion of the IDSA documents. And that is, in this setting, we would use a composite of 15 day all cause mortality and morbidity variables that represent meaningful benefit to patients as assessed by PRO instruments.

And that is, in fact, I believe, a very appropriate strategy but it is a strategy that doesn't give us, at least in view, the ability to formulate a non-inferiority margin. As we use this approach in the future, non-inferiority margins may well become possible.

In the intervening time period, at least in the context of those agents that could also be studied in the severe setting or have an IV formulation that they could be studied in a severe setting, I would consider it appropriate to follow a strategy that I heard Dr. Temple lay out as a possibility.

That is, that when one has completed a study in the severe setting with non-inferiority and mortality, then the label could be given for CAP.

ACTING CHAIR TOWNSEND: Dr. Follmann?

DR. FOLLMANN: So, I interpreted this very strictly speaking, which was, what was the evidence for a placebo versus an active agent in terms of an endpoint that would be suitable for mild to moderate disease. And I didn't see convincing data presented to show a reliable treatment effect for that.

Having said that, though, I think if we had such data, it would be likely that M1, the thing that this question addresses, which I don't think there is adequate data, I think M1 is probably a lot larger than what M2 would be and we would end up being in a position for this setting, just as we were earlier for mortality, which was the margin

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that M1 we could reliably quantify was quite large and we were spending our time deciding what M2 would be.

And so, I am inclined to think the discussion on this should be for M2, recognizing that we don't really have reliable data for M1. And when I am talking about that, I think it is for the clinical failure endpoint. Defervescence, I think, would have substantial problems to use as a non-inferiority endpoint.

ACTING CHAIR TOWNSEND: Dr. Temple?

DR. TEMPLE: Well, you do have to sooner or later, that is what number three is, pin down what you are going to say and why you are going to say M1 is. Then you can work -- M2 is just a judgment call. You can always come up with that. That is easy.

I wonder whether what people are responding to is a little bit like the idea that you can treat some quite sick people starting off with an oral agent and not

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necessarily give them IVs. There are a view that nowadays people about as sick as were in those older trials might very well be treated as outpatients with an oral product because we know our way about things better and that maybe some of those old data apply.

Sooner or later, even if you don't, we have got to come up with what the margin is going to be. And nobody really said much about how to do that. I know what you want to rule out as M2, but how are we going to state, this is what Tom was saying, how are we going to figure out what the effect of the active drug is? I mean, you all sort of believe that there is an effect. I mean, heaven knows I do. But how are we going to be able to put a number on that so that we can have a trial?

I also want to mention that if you are going to work on risk reduction, you actually have to have some failures, whereas, if you are just going to look at the delta, you don't. Just worth mentioning.

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ACTING CHAIR TOWNSEND: Dr. Musher?

DR. MUSHER: At the time the patients come to a physician at the present time, compared to the 1930s, there are, just as you state, many patients now who are being treated as outpatients who, in the past, would have been hospitalized. Because as I mentioned yesterday, just about everybody who had pneumonia, no matter what their severity, was hospitalized in the past. And then of course, what would happen is that how acutely ill they were on the first day would -- and some patients wouldn't get worse because they would just stay and get over it but in others they would be a whole lot worse the next day because no treatment had been given.

DR. TEMPLE: So you would argue those older data on predominately hospitalized very sick, nearly dead people do have some applicability here and that you can assume responsiveness --

DR. MUSHER: The reason I would