of drugs developed years ago.

I trained at Penn in ID, and I remember remarking to Rob McGregor there when we were doing the pharmacy review, the formulation review, it always looked like you had 80 percent activity of your drugs against the pathogens that were being isolated in your hospital, or 90 percent. Well, that's because the old drugs had been tossed out. So there was a false sense of reassurance about how well you were doing.

So let me talk for a minute about undertaking a CAP clinical trial program. And I do want to mention a few things about industry. Industry is a word that's often used, but it's a simplification. Industry is not in fact a monolith, and there are large pharma a biotech; that's one way to categorize it. There are other ways.

But basically these are very differing companies that have different goals, assumptions and constraints. But in my



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experience and my belief, there are some common denominators for pharma R&D, and I've listed them here.

First of all, whether you're in a large company or small company you need to have funding for your projects. In small pharma that may come from venture capital; in large pharma you have to convince your management that they should invest in your program as opposed to an ED product.

There also is a fiduciary responsibility to shareholders. That's there. It's inherent in American capitalism.

And there also is this last one of doing the right things for patient and society. Now as a physician, an ID physician, this is where I start. But as John Rex and others in industry can tell you, you can't do this unless you figure out how to meet these other responsibilities.

This won't happen, so the decisions are complex, and when I look at



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people like John and others, I see a group of people who are really passionate about the need to do the right things for patients and society. Not all of them. There are always exceptions. But this is my observation, and obviously I feel strongly about it.

So what is the context of starting a CAP program? First of all there is a multiplicity of audiences. And this is a group of audiences that are worldwide. We are here today with the FDA, and we appreciate that opportunity, but as drug developers we need to think about regulatory agencies worldwide, and harmonization of expectations and discussion among those agencies is really essential so that companies can know what's expected of them.

We also have these other audiences, all of which are important. All of them have needs that have to be met. You can't bring a product to market and not meet the needs of all these different



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constituencies.

These varying needs, especially worldwide, add risk and uncertainty to the process. And again, today, what I'm asking you to do is as others have done is, from a regulatory perspective, to add - to remove the uncertainty from some of the issues surrounding CAP development. It would be extremely appreciated.

So what do companies want from a clinical trial program? In thinking about this, I thought of three axes. First of all they want the trials and the program results to be credible.

They also want them to be predictable and feasible, and I'll talk to you a little bit about each.

So credibility, there are two subsets there that I can see. One of the scientific considerations. People need to know when they're designing trials are there validated methods and tools available to not



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only design but conduct and analyze these trials?

And I think this gets to one of the points made about PROs. They sound like a great instrument; there is promise there. But as we've heard they are not validated for this indication, and probably not validated sufficiently.

So that places someone considering a trial program in a very difficult situation. How can you initiate a study without an instrument that has been validated scientifically and accepted from a regulatory perspective.

And that leads me to another point which is that we not only have to - we as drug developers, in that hat - have to please not only FDA but also regulators worldwide.

And clearly these trials have to address an unmet need or provide data relevant to current practice. The skeptics and cynics will say that well that's so you can sell it.



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But and that's true, you do need to sell it. But it's also true that that's what it's about for those of us who are interested in patients and societal benefits.

So what about ethical considerations? I think there is another strong component of credibility.

The trial design, any trial design, has to be acceptable to all audiences. I showed you the audiences before. As a drug developer, when I've done that in the past, in a company, it's first and foremost whether I can write an informed consent that will tell the patient what he or she needs to know.

Will the design be acceptable to the IRBs? And I would point out here, with all this discussion about placebo-controlled trials that it's very difficult for pharma companies to be innovators if doing so requires contravening established clinical practice guidelines, or even investigational precedent. It's very difficult.



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You can't go to an IRB with what might seem to them like a wacky idea. So I think an idea today that we have to recognize in terms of guidance is that controversial hypotheses have to be examined, or should best be examined, in non-pharma sponsored trials.

So predictability: well, we had a little discussion about predictability earlier. Again, these slides were written previously. What it is is stacking the deck to assure the results you want.

Does that ever happen? Probably. Is that the core tenet of what we're talking about today, or what the people here today feel? No. What it is is identifying the clinical statistical regulatory and even commercial variables that impact the trial results, and accounting for them carefully in design, conduct and analysis.

Let me give you a couple of examples. Clearly knowing what regulators want is essential. What about clinical



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variables? Well, we talked a bit about the PORT one or PSI one through three, and that maybe companies are studying just those patients because they are easier to get and you know the results.

Well, there's also the issue that PORT five patients are extremely difficult to come by. Most of the exclusion criteria that are required for the guidance, and for good common clinical sense result in exclusion of those patients.

If you have 5 percent of your patients in a trial who are PORT five, and then you were told you needed only to do PORT five, your trial goes - is extended 20 times in length.

So do you want a drug in two years or three years, or do you want a drug in 20 years?

I think the regulatory expectations I want to comment on as well. What the industry works with at the moment is



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guidance that was promulgated by FDA in 1992 and 1998 with industry input, which was appreciated. And Dr. Tom Beam led all of that back in 1992. But what industry is working with with those clinical trial design features that you saw earlier is what's been agreed on.

Now that doesn't mean that I think or anybody else thinks they should stay the same forever. But those have been the regulatory constraints, and if you don't meet those regulatory constraints, your drug really doesn't have a chance.

So it's good we're here today. I applaud the FDA for bringing people together to discuss changes. But they would be changes to what has been required of industry previously.

Predictability is an essential consideration in the trial timelines that are measures in years and costs in millions of dollars. Let me show you a number of trials very quickly here. They range from oral to



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IV. They were started longer ago or more recently, but I have listed here direct study costs. That's what it costs to pay investigators. And by the way I'd mention that that's increasing a lot.

The fully loaded, meaning what happens when you include all your payments for your rent and everything else; patients enrolled, and costs per patient.

A couple of older trials, $19 million, or $20 million for each. So for a program with two studies in CAP, we're talking about $40 million. You add in a couple of other indications you are beginning to reach appreciable amounts.

Each patient enrolled, 36,000 or 30,000. So more recent ones, you see some variability, but in this more recent study 50,000 a patient.

And in this most recent set of data, total fully loaded costs of about $75 million just for two CAP studies, with a



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sample size that is currently resulting from the expected noninferiority margin and the trial design elements that I gave you before.

So I find this concerning and worrisome in terms of where we go from here.

So a lot is at stake. For early stage development I can tell you from experience that venture capital interest is high now, but things can shift like that. And a large part of that is regulatory expectation or prediction.

For phase three, smaller companies can start, but they need a larger pharma partner to get through. A hundred, two hundred million for a phase three product. They need to have a big company that is interested in making this kind of investment.

So the bottom line here is that dollars currently targeted for CAP could go elsewhere. They could go to other indications, other therapeutic areas, even other industries if you are talking about D.C.



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This is not to say that you should go soft on the science. That's not what I'm asking. What I'm pointing out is that decisions and clear advice to help the agency reach a conclusion and a clear conclusion on this is really essential.

There are some compounds at risk on this predictability axis. Several compounds listed here have recently completed phase three trials, or have phase three trials ongoing. These have been started with the type of investment I've mentioned under the previous assumptions. So if we say a couple of hundred million dollars here.

And there are compounds waiting in the wings here, compounds that would be suitable for studying CAP that completed phase two, or are contemplating phase three. And these compounds need certainty for them to receive the support they need to advance.

So what are some of the overhanging issues for these compounds who are



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at risk on the predictability axis? These are the ones we've talked about today in our design outcome measures population studied.

And you've seen some examples of recent CAP studies with margins of 10 percent. A question for you, with populations mostly being in two to four, and I already discussed the problems with five.

And outcome measures that you've also heard about that are based on clinical response and not microbiological response.

This is also a reprise to some extent of what you've seen earlier. This is one study to tell you the impact or the ability of us as developers to come up with culture positive patients.

And I'll highlight here strep pneumoniae which has been a focus of discussion in this study about 20 percent of patients were identified as having strep pneumo, but a little more than half were identified as culture, and the rest about 10

percent of the total patients, but almost 50 percent of those identified as strep pneumo were identified by a urine antigen. And I have to say in all honesty that my impression from discussions with regulatory agencies is that in the past at least this has not been acceptable for defining a case of strep pneumo.

You want the bug, you want to know its susceptibilities. This is my personal experience. So we're talking about 12 percent, 13, 15 percent of all patients enrolled having strep pneumo.

So finally feasibility: are the scientific and regulatory requirements understood, and can the trials be completed within an acceptable timeframe?

Design, including discussions with regulatory agencies, IRBs, et cetera, enrollment, and that depends on sample size, and of course regulatory review, and the question that every company has to ask is,



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will the cost of the trials make sense compared to other options?

So clear regulatory guidance is essential, and ideally if the science permits - I emphasize that - if the science permits - this guidance should not jeopardize decisions made by companies already and made in good faith; that would be my hope.

Let me turn to some major design issues in CAP clinical trials. I think we'll hear more about this tomorrow.

So in contemplating a trial there are a number of key issues. I've put some of them on here and highlighted with an asterisk the ones I wish to talk about in more detail.

They are a spectrum of study drug, dose selection considerations, choice of comparator, et cetera.

So spectrum fo study drug, that sounds pretty straightforward. Does your drug treat strep pneumo, or does it treat H. Flu, or what have you?



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But it's not as simple as that in design. Because you need to potentially cover all the relevant pathogens to be able to study your drug as monotherapy. So the macrolides and fluoroquinolones are efficacious, versus the broad spectrum of CAP agents. But what about the cephalosporins? Ceftriaxone is probably the most prescribed drug for - IV drug for CAP inpatient, but it is not active against the atypical pathogens. And we also in addition to this point have some data, as you heard earlier, showing that improved outcome occurs when you add a macrolide to a cephalosporin for therapy of at least severe or bacteremic pneumococcal CAP.

So in the context of a clinical trial design how do we provide optimal therapy for patients, without an overlap in spectrum that confounds assessment of efficacy?

Speaking from personal experience, this is very difficult. With the cephalosporin there are only a number of



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countries in the world where cephalosporin monotherapy will be accepted as appropriate clinical practice. They are outside the United States; they are outside of Canada. So you have a huge conundrum in trying to study a new cephalosporin for this illness if more clinicians expect that you are going to give a macrolide as well.

Dose selection: I'm not going to go through all of these. Just one point here - two points. Activity in animal pneumonia models, when I put this slide together I thought, gosh, you know, it'd be a lot easier if we were debating the noninferiority margin for murine pnumococcal pneumonia, but unfortunately we're talking about humans here.

But I do want to substantiate John Rex's point that there are a huge number of data showing the efficacy of antimicrobials in well established homogeneous models, and I do find that relevant to the current discussion about whether there is a treatment effect or



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not. It does leave the issue of what the magnitude of the treatment effect in humans is to other discussions.

So we know that science allows prediction of efficacious dosing arrangements, but there are things that we must beware in trial design, and that includes the unexpected, including different pathogens than anticipated, such as MRSA beginning to pop up in your clinical trials.

Choice of comparator: I did participate with IDSA -- this is a disclosure -- in drafting the position paper. Looking at that, listening today, my conclusion still is that there is a substantial consistent antibiotic treatment effect in CAP; that there is historical evidence of sensitivity to drug effect.

It's certainly true for mortality, and I thank Dr. Fleming and Dr. Powers for their additional analysis, which I think adds to that argument.



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I also find it convincing that there is an effect on morbidity, and it's supported by all these data.

And I think if we had the entire totality of the database and the PKPD relations, we would find a lot more information there to substantiate a treatment effect.

The effect size does vary by severity of illness. It's clearly most pronounced in moderate and severe CAP, but I think it's clinically meaningful in mild CAP.

And as mentioned before, asking industry to conduct placebo-controlled studies in CAP I think would be very difficult. I mean in the current environment about how people think about the pharmaceutical industry, frankly, I could not advise a client to undertake a placebo-controlled CAP study. I think there are too many audiences that would be suspicious and would reject that idea, and I think it would ju9st be untenable.



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If this is to be studied, I don't think pharma is the one to do it.

Choice of comparator: we need to exercise due care in comparator selection. I've mentioned the appropriate issues here. And what isn't acceptable, if we were thinking about active control studies, superiority studies, what isn't acceptable is use of a comparator that is sub-optimal re any of these parameters up here. And unless you pick a compound as a comparator that isn't well tolerated or is at too low a dose or isn't efficacious to begin with, I don't think you have a chance of showing superiority in a CAP study, and I think you have heard data there. And there is by the way the multiple comparisons issue with the few studies that did show superiority.

IV or oral switch, very quickly. Standard of care, and I am paying attention to time Mr. Chairman, IV or oral switch, another conundrum. Potential confounding of efficacy



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and safety assessments, something you could discuss tomorrow.

In terms of patient populations, I'd point out that I believe that CAP severity can be defined using what were prediction tools but which can be adapted as a severity assessment tool.

These are feasible for patient trial enrollment, and in particular as Dr. Wunderink mentioned, these are relevant not only to regulatory considerations but to clinical practice, and then where you are going in the end, which is the product label.

If you could align the clinical trials, the product label with clinical practice, I think that would be a big advantage. And I would propose using the PSI as a base, but then adjusting it for other variables, mechanical ventilation, bacteremia at baseline, et cetera, that would allow you to more accurately identify patient severity.

Prior antibiotic therapy, as we've



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heard, artifactually improves response in CAP. The obvious solution, which is to avoid prior therapy, has major logistical consequences, because it excludes huge numbers of patients. We need better approaches to this issue. You could talk about that tomorrow.

I view the most attractive at the moment is to allow a single dost of a very short acting agent, such as cefotaxime, or perhaps an oral cephalosporin and still allow patients into trials, with the hope that in the future rapid diagnostics could facilitate inclusion of nontreated patients only.

Which pathogens? And this is really my last major point here. We know that the data for documentation of treatment effect is greatest for strep pneumoniae, and to a lesser extent, atypicals. There are fewer data for other relevant pathogens.

The problem at the moment, if we want feasible clinical trials today, is that the diagnostic accuracy of the rapid testing



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devices is not there, to allow timely triage for trial entry.

And I'd also mention in clinical practice, the pathogen is often not known, so in a sense there is some relevance there.

If we were to restrict primary trial analysis to typical pathogens only - strep pneumo, H. Flu, MCAT - we would at least double the clinical trial sample size, roughly. If strep pneumo only, the sample size would go to perhaps four to fivefold, the required sample size now, if you with the current assumptions, if you require culture positive it migh8t be somewhat less than that.

So certainly this is an important consideration for you to bear in mind when you think about what population you are going to require to be included in trials. It's all data based on clinically defined populations are useful to clinicians, and generalizable, and logistically retaining clinical criteria for the primary evaluation is desirable.



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I'll summarize with the NI margins. I believe these are justifiable. Moderate to severe with a dichotomous outcome. A 10 percent delta that could be mortality or mortality plus. Mild CAP, I could see changing this. I think some of the arguments today suggest that we might have a problem with the most mild cases, but for other mild cases with other measures of severity, a 5 percent delta might be appropriate, but 10 percent delta for time to events could be quite reasonable if one is talking about defervescence, feeling better, discharge, et cetera.

I believe that a superiority design is not a feasible nor justifiable for registration trials. Patients enrolled in these studies would have - would be enrolled with little chance of the trial meeting its endpoints. That would contravene a major ethical consideration in my view in asking a patient to participate in a trial. If the



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trial has no hope of meeting its endpoint, then any risk is too much. And I think you'd also be worried about exposing them to a suboptimal comparator.

Because of time I'll just mention that the relevant outcome measures have been identified. We've discussed those. We'll come back to them. A key issue of course is validation of the instruments, specifically, for mild to moderate CAP.

So in conclusion, and I thank you for your attention and forbearance with my time, society will benefit from the availability of new antibiotics for treatment of CAP. These are not going to be just for CAP.

And it's occurring in the context that resistance is increasing, and we have to recall that the decisions taken today determine our options in 2015.

We in industry as well as you in academics and you as regulators want trials to



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be credible, predictable and feasible, and industry needs updated, clear and specific guidance to do that.

Substantial treatment effect has been established. I've talked about superiority design, and why I feel that placebo controlled trials as registration trials would be very problematic, as would active control trials, and I do feel that an NI design is scientifically appropriate as well as logistically feasible.

With the NI design being such that the patient populations can be defined readily, and as can outcome measures.

With pathogens I'll just leave you with the thought that restricting trial analysis to micro subsets will add lots of time and cost the trials.

So how could the advisory committee help? I would ask you please to consider the proposals based on both their scientific merits and the ability of companies



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to implement them so that new drugs will be available to the patients who need them; make the best possible balanced decisions today. I'm sure knowing all of you now that they will be perfect, but on the occasion that they might now, I would submit to you that decisions now will always be revisited, and should be revisited, do the best you can today so that trials can move forward. And please help our FDA, all of us, to give prompt, clear guidance for antibiotics waiting in the wings so that FDA and industry and academia can facilitate the development of safe and effective new CAP therapies.

Thank you.

ACTING CHAIR TOWNSEND: Thank you, Dr. Talbot. We have about half an hour for questions for Dr. Talbot or for any of the other speakers who have gone today from the panel members

QUESTIONS/CLARIFICATIONS

ACTING CHAIR TOWNSEND: Dr. Dowell.



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DR. DOWELL: Could I reraise the issue that was raised earlier? It seems like there is a branch point here, the difference between an absolute difference or absolute delta and relative delta.

Maybe I have it wrong, but it seems to me that that would drive a lot of the discussions later on if we are going with what we have been talking about, an absolute difference; it seems like we are going to be talking about a whole different kind of patient than if we talk about a relative difference. Is that not a decision it would be helpful to make early on?

ACTING CHAIR TOWNSEND: That is probably a legitimate question. I don't know, Ed, if you have any comments on that, or Dr. Fleming?

DR. COX: I can comment on this. I think Tom addressed this, and it's the issue of how many events will occur. If the rate is lower then it sounds like it's a situation



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where you'd probably need a fair number of patients if the patient population has an event that is occurring at a fairly low rate.

So I think Dr. Fleming summarized it well where he talked about how conceptually this is probably something that -- or may be something that is going on based on what we're seeing in the data. The question then is, where does that leave you with regards to how many events would occur depending on the type of population you were looking at.

But it is a critical question. Others may have other comments on the issue.

ACTING CHAIR TOWNSEND: Dr. Weidermann.

DR. WEIDERMANN: Well, I was going to -- and I'm sorry Dr. Musher left, because I think that discussions starting with Dr. Calhoun and Musher and Fleming, and I was a bit alarmed, because going from absolute risk reduction to relative risk reduction, it seems like especially in the talk applying to



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pediatric patients where we're bypassing the idea that the lower level of the confidence interval would be sort of the starting point to figure out where the noninferiority margin is. And it seemed like those in the discussion were saying, well, let's just assume something from adult studies would carry over to pediatrics. We'd have to ignore that lower limit of the confidence interval because the number of pediatric patients in the ancient trials is too small. We know it's going to cross zero.

And that seems to go against everything we should have learned about studying drugs in pediatric patients, is that when we extrapolate as if they were little adults we end up making a lot of mistakes.

So to me it's almost better not to have any study than to say the FDA has approved this drug for use in pediatrics, because it's a toss up whether going that route for information is really going to be



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valid.

ACTING CHAIR TOWNSEND: Dr. Whitney.

DR. WHITNEY: Yes, just to expand further on this line of discussion. I think it's starting to worry me that if I'm understanding what everybody is saying that we almost need different margins for different age groups and different outcomes; and whether a patient is bacteremic or non-bacteremic, and maybe there are some that should be the first priority to set, and maybe from those we could come up with some rationale for addressing these other groups.

ACTING CHAIR TOWNSEND: Dr. Temple?

DR. TEMPLE: In cardiovascular medicine people generally use hazard ratios. And the reason for that is, they are afraid that the environment has changed with respect to the rate in the untreated group.

So you might have thought that people after a heart attack 20 years ago had



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a 12 or 13 percent mortality, and for various reasons you know think it's 4 percent. So what seems likely to be constant is the effect of a drug on the hazard ratio. That is not proven, but there is a belief to that effect; whereas if you -- if the rate of events has gone way down you'll never rule out the absolute difference from the past.

My impression from hearing people talk here is that they believe things are at least enough constant so that for the same organism, same degree of illness, same kind of patient, what happened in the past before there was treatment would happen now if you left them untreated. I'm in no position to evaluate that. But that makes using the past absolute effect quite plausible, and I don't see how there's much gain from going to percent reduction or hazard ratio, because in this case everyone seems to agree that the effect size in at least the severely ill is pretty large, large enough so that you can



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take a portion of that and say, I don't want to lose more than this anyway, and be very very sure that M2 is smaller than M1, and if you are sure of that, you're done. You know what to do.

So what seems to me in some of the conversations is getting lost though is, that for the study you are going to do, you have to have a belief in knowing what the effect of the active control is, which sort of means for one thing it probably needs to have been studied, unless you are willing to say, oh, it's just the same in all these other people anyways on whatever grounds you can. But you have to know what that is.

So moving to populations that haven't been studied and are very different, there is no way to do that and still believe you have HESDE. That's the trouble. I think Tom laid that out pretty well.

So getting into milder illness, unless someone can give you good data on



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resolution of febrile state or something from past experience, there is no way to do that. It's not that it's a stupid endpoint; it's that you don't have the historical experience to use it.

I mean I have to tell you we are facing this all over the building, mostly in cardiovascular things, where no one is willing to leave anybody untreated anymore. So noninferiority is the name of the 21st century game.

But the crucial thing is knowing what you can say for sure the control drug would have done in that study. So it's very hard to move past where you have good data on that.

ACTING CHAIR TOWNSEND: Excellent point, thank you.

Dr. Follmann.

DR. FOLLMANN: So just getting to amplify on that point a little bit, so you know, based on the idea of a physician paper,



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they report historical rates for different groups of the PSI index, and they range from 1 percent to 17 percent, and they have on their table of margins a trial maybe with PSIs from 2 to 4 or 5, and a margin perhaps at 10 percent.

Now if you end up enrolling people in that trial who are mostly PSI 2, you'd have a very low mortality rate, maybe 2-3 percent, and a 10 percent margin just doesn't make any sense there whatsoever.

So you know, maybe you are bold enough to say, well, we know what kind of patients we would enroll in this study, and we can a priori know that we would have a 10 percent or a 20 percent mortality rate. But failing that, you could get surprised. And it's happened in the past, or you get a much lower mortality rate, and then you have a very large margin, and you have a trial that doesn't really make sense.

I don't think it makes sense to



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say, okay, the margin is 10 percent; there is a 1 percent mortality rate in the study, so we're okay with a tenfold increase in the risk. So it has to be very - you have to have very good knowledge or expectations about what the mortality rate will be in that future trial.

And in mild CAP, if we are looking at mortality as an endpoint, you know, it was mentioned earlier, we would need small margins. And you know they might be so small the trials would be undoable.

But I don't quite see a way around that if you are using mortality as an endpoint.

DR. TEMPLE: But the proposal that I heard coming from Tom and which sounds right to me is, you pick people who aren't low risk; you pick people who are high risk. That's who you put in the study, and if there is a range of great two to four or something, and you are allowing them in at all, you make sure they



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are not more than 5 percent or 10 percent, and you look part way along to see who is getting into the trial, because you don't have any information about the effect of the old drugs, or you don't have enough information to pick a margin. You don't have enough information in those milder illness. You need to have the relatively sick people.

I mean I'm a little worried about the effect of giving a single dose of an antibiotic. I don't know what that does to the historical estimates, but let's say you can get over that.

But you - the trial has to say this is for sick people.

DR. FOLLMANN: No, I would agree with that. It just makes a more difficult question for people with mild CAP, what do we do with them?

DR. TEMPLE: Well, we've been talking about that a lot. And I believe I said this at the workshop, personally, but I'm



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not burdened with being - having any knowledge about infectious disease, so take it with that into account, if you knew that a drug worked in people with very severe pneumonia who were fragile, it seems perfectly obvious it's going to work in people who are less ill. I mean the benefit will be smaller, because their risk is smaller.

But one of the things that probably needs to be discussed tomorrow is, if one would apply the indication broadly to all severities of pneumonia if you knew it worked in severe pneumonia.

Because from the sound of it, in these relatively mild things, you are not going to be able to do a noninferiority study because you don't have the data on what the benefit is in them. But surely if it works in very severe pneumonia, it works in less severe people; that must be true unless I'm just missing something.

ACTING CHAIR TOWNSEND: Dr.



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Fleming, did you have -

DR. FLEMING: Well, I sort of had a stupid question for anyone. I mean it's too bad we're hampered with these historical studies, that only report mortality and make it difficult to get at these other endpoints. But if I were doing a systematic review on studies nowadays, and an article was published and it didn't have all the information I needed, I'd then call the author and see what information is available.

And I'm not suggesting a seance. But when we talk about Max Finland and people like that, has anyone checked to see if in some vault somewhere there are archives of his study notes or things, and maybe this information exists, and nobody has asked for it.

ACTING CHAIR TOWNSEND: Dr. Cox.

DR. COX: Yes, as far as I know we haven't contacted the authors of historical papers, and we have searched around as much as



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we can to get papers from the archives.

And I don't actually know which are still alive and which are not. But we've tried to do what we can to get as much data as we can, but I'm not sure how much more of that -

ACTING CHAIR TOWNSEND: Dr. Temple.

DR. TEMPLE: Well, there is another factor, of course, and that relates to the constancy assumption.

You can have a fairly strong belief that mortality was assessed then more or less the same way it's assessed now. But some of these other things which - I mean I don't know much ID, but I'm sure that's true - but you've got to be less sure about that when you get to these other endpoints, which may not have been very well specified, and so you are uncertain, even if you could find files, your uncertainty about whether that's the same as now, and whether it's really relevant, has to get larger.



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Again, that's another of the problems. You know, in cardiovascular ones you have death, MI and stroke, and you feel pretty good about that, and then they'll say, unstable angina. Well, who knows what they mean?

So the more uncertain, the more less defined the endpoint is, the more difficult it is to be sure you have.

ACTING CHAIR TOWNSEND: Dr. Rex.

DR. REX: I want to make a comment about the use of the PORT or PSI scoring. And I'd like to read to you from the ATS guideline documents, a brief passage, but let me read it to you.

For example, a previously healthy 25-year-old patient with severe hypotension and tachycardia and no additional pertinent prognostic factors will be placed in risk class two; whereas a 70-year-old man with a history of localized prostate cancer diagnosed 10 months earlier, and no other problems,



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would be placed in risk class four.

However, even a patient who meets criteria for risk class five on the basis of very old age and multiple stable chronic illnesses may be successfully managed as an outpatient.

So I want to make the comment that the PORT score and the CURB score have some quirks with respect to estimating severity. However, it is helpful to recognize that there is one thing that runs through the middle of all this, which is the pneumococcus. Pneumococcus is a surprisingly virulent organism. We have lots of data to suggest that even young folks with the pneumococcus can get into a lot of trouble without treatment.

And if you read the old papers, and actually I did, like Dr. Fleming, I pulled them all, and I read them all.

It's interesting to find out what it means to survive with untreated CAP in the



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old days. I pulled up one a few minutes ago where it talked about the patients were still having their empyemas drained. And then they talked about how after the introduction of antibiotics we no longer saw empyemas, and the thoracic surgeons were kind of bored.

So it's worth recognizing that it's - that the pneumococcus gives us a really strong platform for identifying efficacious agents. It's a very virulent organism, even when it goes away on its own; even when you survive, you can be left with major complications without therapy.

The current era of most physicians never having seen a pneumococcal empyema is one which reflects the fact that almost everybody gets treated.

So I'll just make that observation. It's a combination of the issue of severity markers which PSI really is not - it's got issues - with the fact that the most important organism is a very virulent one by



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any measure, and that actually gives us a very powerful set of tools.

ACTING CHAIR TOWNSEND: Dr. Fleming?

DR. FLEMING: Maybe let me try to comment further on this issue of relative risks and absolute differences, and just to try to make it efficient, I concur with the points already made by Bob Temple.

Sometimes it's useful to think of what's happening in other settings, because often we are confronting issues that are not entirely unlike what we confront in medical practice in many other areas.

So in the world of atrial fibrillation where coumadin or warfarin is standard therapy, there is keen interest in alternatives to that, where you don't have to have the intensive ion monitoring, and you don't have to have the risk of major bleed, so there is a lot of interest in other interventions which would, like coumadin, be



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very effective in reducing stroke.

So a drug was studied and I was serving on a cardio-renal advisory committee a few years back as it was being reviewed. And essentially there was an expected 3 percent mortality, and the sponsor had defined an absolute margin of 2 percent, which is a relative 1.67 increase.

And when the study was completed, the actual stroke rate wasn't 3 percent in warfarin; it was 1 percent. And having an absolute 2 percent increase now would have been allowing a tripling, not a 67 percent relative increase, but a 200 percent relative increase; and the advisory committee said, no. That's not a rational upper bound for ruling out that my alternative to warfarin isn't going to be losing some of the important benefits on stroke.

And so essentially what's gone forward, what is the standard at this point, is that relative risk is being used, and the



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relative risk we have to rule out is around 1.38 to 1.45, that's what sponsors are using.

That translates to studies of about 6,000 people. That's the norm. That's the norm as you are looking at a new intervention in atrial fibrillation is to rule out about a 50 percent relative increase.

With the COX-2 inhibitors that provide very important symptom benefit and reduction in GI ulceration in - compared to nonselective NSAIDS, the precision trial now is being done to look at a COX-2 against Naproxen to rule out a 33 percent relative increase - not a 67 percent, a 33 percent relative increase, 500 events, 20,000 people.

The big issue now, there was an ODAC, there was a cardio-renal committee recently on erythropoetins that had been used for an extended period of time, for what? Basically what we know is that we get a reduction in transfusions. That's a pretty significant impact on the national blood



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supply. Kind of I would say at least as important as reducing time to becoming afebrile.

And in that context though, while it was thought end stage renal disease and in chemotherapy induced anemia, that this could also translate into survival benefit, now there is evidence that venous thrombotic events are occurring, and it's actually translating into an adverse effect on survival.

So when the intervention that you are giving isn't just being given for afebrile status, it is important to understand - we are asking now why have we had such an extended period of use with erythropoetins, before we actually understood what the effect is, more than on reducing transfusions.

So essentially, if we return to our setting here, to support what Bob was saying, if you target a population that has a 15 percent baseline mortality, and you are



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ruling out a 1.67 relative risk, a 10 percent margin - by the way that's a really healthy margin compared to what I see in other clinical areas when you are talking about mortality - we are talking a study of 500 - 550 people, not 6,000 as you typically would be looking at for any agent that is looking at an alternative to coumidin or warfarin.

Now the point that we were making, and Dr. Calhoun made a really good observation, and that is, if you look at these data, it may well be that if you look at it as a relative risk, you might have a common margin.

So Dr. Whitney, yes, the data clearly say, if you look at an absolute difference, the margin absolutely depends on the risk level.

Now if you translate into a relative risk model, you might be able to come up with an upper limit margin like 1.67 that you could uniformly apply, but now if you



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apply it to a population fo young people that are at low risk at a 1 percent mortality, this is going to be a 10,000 person trial.

And it's also based on the assumption that is not proven at all that the potent effects that we see when you have a high risk of mortality will translate in a relative risk model, and you need hundreds of events to be able to validate that.

So if you are willing to make that assumption, we could go to a relative risk model. But you are going to pay the price of doing an enormously large trial, because basically you need 100 to 150 events. To rule out a relative risk of 1.5, when you truly have no difference, it takes about 100 to 150 events. Well, if you are putting a population on that has a 15 percent mortality, you are going to get that with 550 people. If you put it on with a population as 1 percent mortality, we are talking 10,000. We are talking about what you are doing right now



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when you are trying to establish the safety of celacoxib as a COX-2 inhibitor where it's 20,000 people, or an atrial fibrillation agent that is going to be used instead of warfarin where it takes 6,000 people.

We are trying to actually make it easier here to keep it to 5 - 600 people.

ACTING CHAIR TOWNSEND: Dr. Whitney.

DR. WHITNEY: Just to follow up on that, is it possible that we then need some different outcome for those young healthy populations? And if we don't have the historical precedent, what do we do about getting new drugs for children?

DR. FLEMING: That is a discussion for tomorrow, right? That's an extensive discussion. Dr. Temple has put forward one way forward on that, and I assume we are going to talk about that tomorrow.

ACTING CHAIR TOWNSEND: Dr. Dowell.

DR. DOWELL: So if I'm



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understanding the conversation, it seems like we are moving towards trying to enrich trials for more severely ill patients. And I had a question that I think relates to that.

It was in Dr. Nambiar's presentation, and I wanted to make sure I understood it. You talked about the fact that a number of these trials have shown no difference between the new drug and the comparator drug, with the one exception of the daptomycin trial it looked like in that trial when you looked at the PORT scores of those enrolled, the numbers were 42 percent class two, 30 percent class three, remainder class four. Which is about 27 percent that would be class four, or I thought you said one was class five

By comparison you said of the other comparable trials about 20 percent were PORT class three or four, and few were PORT class five.

So my question is, does that mean



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that the one trial that showed a difference was really enriched for class four patients with respect to most of the other trials. Is that correct?

DR. NAMBIAR: I don't' think there was any specific strategy that was utilized just to enrich the particular study to involve patients with PORT scores of four.

DR. DOWELL: But it just happened to come out that way?

DR. NAMBIAR: Yes, the patients with PORT scores of two to four could be enrolled. To the best of my knowledge there was no particular enrichment strategy that was used for that particular study. It was all in hospitalized CAP patients.

ACTING CHAIR TOWNSEND: Dr. Musher.

DR. MUSHER: Wasn't the daptomycin study was designed to study patients with staph aureus infection, which is just a more severe disease. Isn't that the answer? No?

DR. NAMBIAR: The gram positive, so



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both strep pneumonia and -

DR. MUSHER: Okay, sorry about that.

DR. NAMBIAR: And also microbiologically documented infections, large majority was strep pneumo.

DR. MUSHER: Could I make another comment about the etiology of pneumonia? Dr. Nambiar and I talked about this briefly during the break.

First there was a very nice study on community-acquired pneumonia reported in JAMA in 1997 and `98, in which it was done at the Mass General and maybe at Providence, and there was a large number of patients.

In 16 percent of patients an attempt was made to establish a bacteriological etiological diagnosis by submitting a sputum sample, and in half of those a diagnosis was made, and most of them were pneumococcus, and the rest were H. Flu and a couple of more, et cetera.



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And I think that's the kind of number that most of do continue to have in our mind. Even a lot of the outpatient pneumonias, fair number of them are pneumococcus.

Now Dr. Nambiar shows us a study - shows us a summary of studies in which there were those round bars, and it looked as if an etiological agent was determined in 60 to 70 percent of in each series, but only a little teeny-tiny number of them were pneumococcal.

And I do want to point out, and I think Dr. Nambiar agrees with this, that the documentation of the pneumococcus was by culture, and the documentation of the other things were serological, many of which are highly questionable.

In fact as recently as just last year, a very nice paper in CID said there is no valid serology for a chlamydia infection, and yet a lot of those guys under the quote atypicals, they list them as chlamydia



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infection.

And even for the mycoplasma infection, nobody is taking no sera, send them out prepared, running the same lab as the acute and the convalescence. It's just very questionable diagnosis.

So I just want to point out that it's not as if there is a lot of proven diagnoses that are proven to be something else, and only a little teeny-tiny fraction of them are proven to be pneumococcus. I think there is a lot of unproven diagnoses, in some substantial percentage of those are pneumococcus.

ACTING CHAIR TOWNSEND: Dr. Rex.

DR. REX: Thank you.

Dr. Fleming, I wanted to clarify, be sure I understood your intent in your presentation, because you put up a very provocative slide. You said all this work on one slide, it's a good slide. And in looking at this slide which shows your suggested



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margins, you get the bacteremic and the non-bacteremic in different age groups.

If I am following you correctly, what you are arguing is that there are two - I can see sort of two trials that I can do out of this. One would be, just enroll people over 50 with the pneumococcus, and if all I did in doing that was then compare, as sort of a primary outcome, a mortality-based outcome, using a 10 percent margin, it should take me between 3 - 600 subjects to do that. It's not an extraordinarily large file.

The other way to go is to go down the left-hand column, which is simply to enroll people with bacteremia, regardless of their age. And by the way these are both - without respect to severity, and that's the thing I wanted to check with you, that your view would be that given what we know about the virulence of the pneumococcus, the history with that organism untreated, that those two groups are striking enough that the effect is



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so overwhelming of antimicrobials that those relatively simple designs would provide compelling evidence; is that correct?

DR. FLEMING: Mostly, but the other aspect that I commented, that I mentioned, was that this analysis, while it was making an attempt to adjust simultaneously for bacteremia and age, still it wasn't possible to directly adjust for a number of others, and the Tilghman-Finland article mentioned seven; and there are five others including presence of comorbidities, that also could be significant confounders, and in fact modifiers, that this analysis wasn't able to address.

What it showed, though, and it confirms a sense that people clearly have, and that is the antibiotics are highly effective in these high risk patients. And so when we characterize the patients as Finland did in his major article in 1943 by bacteremia and by age, then we were able to justify that a 10



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percent margin clearly would be appropriate, where, when we did so, the baseline, the treated mortality rate was still at least 15 percent.

So the only caveat to what you're saying is, it would be possible to day to identify a cohort of people that are bacteremic, and particularly a cohort of people that are over the age of 50 that could have less than a 15 percent mortality.

And if you selectively did so, and got a very much lower mortality, then you are extrapolating beyond what the data rigorously allow us to establish. Maybe that extrapolation is somewhat reasonable, but if you did, the argument that's being given then is, we should stick with the relative risk of 1.67 so that if the mortality rate was 10 percent rather than 15, the margin wouldn't be 10 as it is with 15, it would be 6-2/3 when it's 10, which is the same argument that the cardio-renal advisory committee went through.



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The study is still viable. It would then be half again as many people. It's a thousand people instead of the 550 people.

Now you are asking for this extrapolation that the same nature of benefit would apply if you had a selected cohort that was matched to what we did in age and bacteremic, but potentially wasn't matched in several of these other risk factors. But if we make that extrapolation then you would still be using a relative risk of 1.67 essentially, and the study would require a somewhat large sample size.

ACTING CHAIR TOWNSEND: Dr. Kauffmann.

DR. KAUFFMAN: Unless he wants to talk about that, then he should go ahead.

DR. CALHOUN: I was just going to ask for a little FDA guidance on this matter then. If the notion that Dr. Temple was talking about, that is if the agency is comfortable in extrapolating efficacy from



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more severe disease to less severe disease, then maybe the question of whether you need 1,000 patients or 5,000 or 6,000 patients to show a mortality effect in rare event subsets is not relevant.

Maybe we don't actually need to do that. You can show the mortality benefit in subsets where there is a mortality signal, but that's actually an agency interpretation issue, so that's why the question.

DR. COX: And that is one of the questions that we have for discussion for tomorrow. It's actually question number three.

And certainly one of the things that I'm sure will come up here will be the type of formulation that one would need to have to study sicker patients, which would typically be an IV formulation. And then what you would learn from those studies.

ACTING CHAIR TOWNSEND: Dr. Kauffmann? No?



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Dr. Patterson, did you have a question?

DR. PATTERSON: Well, I was just going to comment that while the patients with severe disease, and certainly bacteremic disease, it's easier to show a difference, I think we are going to have to find a way to look at moderate disease, because not everybody has pneumococcal pneumonia that has community-acquired pneumonia. So we are going to have to find some way to assist the atypicals, because it's a different treatment.

ACTING CHAIR TOWNSEND: Well, we are past quitting time here. So unless there is a burning question that we probably won't discuss tomorrow, we'll adjourn. We'll have obviously a lot of time to discuss these and many other questions tomorrow. See you all at 8:00 o'clock.

(Whereupon at 5:05 p.m. the proceeding in the above-entitled matter was adjourned.)



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