resolution of chest pain, resolution of malaise and duration of hospitalization.

For the morbidity endpoints, as a general rule, the margin is probably going to be on the order of 15 percent. For defervescence, it may go up to 20. For mortality it's going to be 10 percent.

So depending on which of those you put into your composite, and how you weight each individual one, that's going to tell you what the margin should be for your particular study.

We did not feel comfortable limiting industry's ability to set -- or FDA's ability to set or govern what the composites should be.

The point really is, this is a general guidance, and that in your individual study, depending on which components you include, you need to justify it based upon the historical data.

This is a typo, sorry, this should

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be number four. So it's the final question we will ask. What about appropriate outcome measures?

A comment about mortality that is derived from the workshop, three specific points were made. The first is that attribution of causes of mortality is likely to introduce bias into the analysis, and it's not clear how accurate it is. So, in general, IDSA favors an all-cause mortality endpoint rather than an attributable mortality endpoint.

Furthermore, review of the historical data suggested that most patients who die of pneumonia, die within the first two weeks, and therefore, deaths after the first two weeks are more likely to reflect underlying disease, so we would recommend a mortality endpoint at around two weeks or so, rather than 30 days.

And finally the point was made, I think, quite compellingly by John Powers, that

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we should not be excluding patients from the endpoint who die in the first day or two after enrollment.

Clinical morbidity endpoints we've already gone over: resolution of fever, cough, dyspnea, chest pain, malaise, duration of hospitalization. As Dr. Alexander touched upon, there was enthusiasm at the workshop for starting to explore the use of patient-reported observation instruments, because they eliminate potential observer bias in recording of objective data.

Of course if you are going to use these instruments, they have to be validated before the trial, and there is an FDA guidance available to help guide the validation process.

So the main points are: that placebo - from the IDSA perspective - is that placebo is not appropriate for CAP trials, that noninferiority studies are appropriate for CAP of all severity, and that antibiotics

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are highly effective for community-acquired pneumonia.

Risk stratification with PSI can allow us to fulfill the constancy assumption. All-cause mortality and morbidity endpoints are appropriate to include in a composite endpoint, and the appropriate margin for that endpoint ranges from 10 to 20 percent, depending on which components are included and how much weight is given to each endpoint.

And I'm going to now turn it over to Dave to bring us home.

DR. GILBERT: Thank you, Brad. This is Dr. Gilbert again, with a few final thoughts.

Knowing the risk of significant morbidity and mortality of pneumococcal pneumonia, as Brad just summarized, the IDSA is firmly opposed to placebo-controlled trials of community-acquired pneumonia of all degrees of severity.

One point that I don't think has

been mentioned yet is the need to plan for new anti-bacterial requirements, not just for today or next year or next three years, but for decades, as the resistance patterns are inevitably going to look worse and worse and worse.

Industry commitment to discovery and development of new anti-bacterials is presently at a low ebb. I think that has been documented repeatedly.

Even with clear, reasonable, scientifically defensible guidance, rejuvenated discovery and development will not bear fruit in terms of bringing new drugs to market for at least 10 years. So what's decided here today will have quite an impact.

The IDSA views the current situation as a public health emergency. The time to remove the uncertainty from the design of clinical trials for community-acquired pneumonia is now.

We think that we have the tools to

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solve the problem. As Brad nicely just reviewed, with our recommendations for noninferiority trial design with reasonable margins, severity stratification, and a reasonable application of the tools of molecular diagnostics as they become available -- and using those that are presently available -- and using reproducible treatment endpoints.

And then, just as an editorial comment, I don't think we should wait 10 or 20 years to go through this process again, because the accrual of data is very, very rapid, and hopefully within three to five years, this advisory committee again will review community-acquired pneumonia trial design, because certainly, we'll have additional information and we will, in a prospective way, eliminate the uncertainty that plagues development of new drugs.

With clear, decisive action, the FDA can remove the current uncertainty that is

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a major, if not the major, disincentive to development of anti-bacterials.

I think everybody in this room is on the same page. We want to take the proper action. In the meantime, the public, and most importantly our patients and the physicians that are caring for them, are waiting, watching and hoping.

We thank you for allowing us to make the presentation.

Mr. Chairman, are we going to have questions and answers, or no?

ACTING CHAIR TOWNSEND: We are waiting until the question and answer session.

Thank you very much, Dr. Spellberg and Dr. Gilbert.

We are actually running ahead of schedule this morning, so we are going to take a break. But we are going to come back from the break early. We'll restart at 10:00 o'clock here.

A couple of things before we

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break. Remember that we should refrain from discussing what has gone on in the session this morning while we are out there. And I think that's it.

So be back here at 10:00 o'clock. Thank you.

(Whereupon at 9:37 a.m. the proceeding in the above-entitled matter went off the record, and resumed at 10:01 a.m.)

ACTING CHAIR TOWNSEND: All right, thank you. If we can all take our seats, it's about time to get started.

Before we get started, Sohail has a little information for us, and then we'll get cracking.

EXECUTIVE SECRETARY MOSADDEGH: Good morning. The FDA media contact, Christopher Kelly, was out earlier. He is here, standing up, if anyone has any questions, I'll refer to him. Thank you.

ACTING CHAIR TOWNSEND: All right, thanks.

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So we'll go ahead and get started. Our first presentation will be from Dr. Richard Wunderink, who will be presenting the American Thoracic Society/American College of Chest Physicians statement.

ATS/ACCP STATEMENT

DR. WUNDERINK: Well, thank you for inviting the ATS and the ACCP to offer a perspective on this very important issue.

I want to start to - by applauding the agency's attempt to improve the quality of clinical trials for community-acquired pneumonia. The ATS and ACCP strongly endorse this, and we also strongly agree with concerns about the need for new antibiotics as expressed by our IDSA colleagues, especially the need for new classes of antibiotics, and we agree that the epidemic of resistant pathogens is something that is incontrovertible, concerning and, as mentioned, is unlikely to diminish in the future, and therefore, we actually are very

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supportive and thankful that we get to go behind the previous presentation that illustrated most of the issues, and I would say we agree with most of the comments that were just made.

The ATS and ACCP perspective on this actually though wants to emphasize a couple of themes that have not been emphasized so much in the previous workshop nor necessarily today, and that is to make clinical trials for community-acquired pneumonia clinically relevant and, as part of that, to be consistent with the most recent IDSA-ATS CAP guidelines.

And I'm going to develop both of those points somewhat.

The first point I want to suggest is that the stratification and definition of types of community-acquired pneumonia be more clinically relevant. And the way that clinicians think, the way that the guidelines are actually set up, is actually to break it

into three categories of mild being outpatient community-acquired pneumonia; moderate being patients hospitalized but not in the intensive care unit; and severe being ICU admission.

In much of the discussion in the literature has talked about moderate and severe as being patients that were not admitted to the intensive care unit, and that is just not very consistent with clinical care.

There is very little difference between PSI 3, 4 or even 5 in patients who are not admitted to the ICU. In particular, there is no difference in microbial etiology there, as opposed to severe community-acquired pneumonia where there is a difference, not necessarily in the actual bugs that cause pneumonia, but in the frequency.

These are a variety of studies of severe community-acquired pneumonia, generally meaning they were admitted to the intensive care unit. And what you see is a skew that

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goes way away from strep pneumonia, into some of these things that include enterobacteriace, staph aureus, nonfermenters like pseudomonas and Acinitobacter. So there is a clear distinction between severe CAP and non-severe CAP admitted to the hospital.

Conversely, the use of the PSI score doesn't really separate etiology. And the PSI score itself does not predict who should be in the intensive care unit. This is just a look at a large series of patients by Angus, and the patients who were admitted to the intensive care unit, 27 percent of them actually were in PSI classes 1 through 3. So it's not - it's really designed as a decision tool for admitting patients to the hospital. It doesn't function very well as a tool to admit them to the intensive care unit.

Now I make these comments about the PSI system not to take away from the previous presentation about the constancy principle; I think that's still very valid.

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But if you are going to design clinical trials, we would suggest that in fact the PSI not be used to stratify patients, but that you use a much more clinically relevant stratification.

The fact is the decision to go to the intensive care unit, we don't have good criteria. Our previous ATS, the revised ATS, the previous BTS, and the PSI scores both including 4 and 5, or just 5, are very inaccurate for that. Some are overly sensitive here -- that 60 percent of the patients admitted to the hospital with CAP would meet criteria to go to the intensive care unit.

And some of them - all of them are relatively nonspecific, so if you meet the criteria, the number of patients that actually get admitted to the intensive care unit is a distinct minority, never getting any better than 26 percent here.

And so the new set of guidelines

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actually rejected all of these previous ones, and went to a newer regimen that took account of some very obvious reasons to go to the intensive care unit - mechanical ventilation and septic shock.

And then a variety of minor criteria that includes things that were in the CURB score, previous things that were part of the ATS score for that.

So we think that this is probably a little bit more valid as far as stratification. And most of the pulmonary, and especially the critical care side of people, cringe when you talk about severe CAP and it not being in the intensive care unit.

So I think that that is much more clinically relevant. And as we go ahead with studies, I think we need to probably define these a little bit different.

Now that being said, the reason I spent some time emphasizing this is because the consistent message I got from all of the

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ATS and ACCP people is, we need studies of severe community-acquired pneumonia. We need studies of patients admitted to the intensive care unit.

This is our recommendation for, in the last iteration of the guidelines, for patients admitted to the intensive care unit; and it's a Beta-lactam specifically cephalosporin, plus a macrolide or quinolone. This is essentially expert opinion, because in fact the only study that has come anywhere close to studying treatment of patients with severe community-acquired pneumonia we could only find one randomized control trial. This was a comparison of ceftriaxone Oflox, and my residents don't even know what that drug is anymore, versus Levofloxacine, and they allowed patients who had mechanical ventilation into the trial.

The overall population, there was no difference. We ended up focusing on this small, not statistically significant but

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bothersome difference in mechanically ventilated patients to say, we still need combination therapy. It's, frankly, all expert opinion, and I think we have to recognize that the only people who are doing studies of treatment for community-acquired pneumonia are the pharmaceutical industry in response to FDA requirements.

So we would highly and strongly recommend that, in fact, severely ill patients be admitted to these clinical trials and actually that they be encouraged.

Now one of the other things that we felt was important to bring up that didn't come up in the previous workshop and is a critically important thing, we think, for the safety of patients is this whole issue of health-care associated pneumonia.

We actually -- long ago the IDSA and ATS broke that out, and we no longer talk about health-care associated pneumonia in our CAP guidelines, even though these are patients

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who are admitted to the hospital from the community, and in previous studies might have been in our community-acquired pneumonia studies.

And the suggestion is, here, that patients - these are the risk factors for multi-drug resistant pathogens. The reason we took them out is, because they look more like our hospital-associated pneumonia, and we thought that the antibiotic regimens for these patients ought to be different than the usual community-acquired pneumonia.

And this is the list from the table that we put in there, and there are things that were the traditional -- like current hospitalization or two days of hospitalization in the previous 90 days, that was a routine exclusion in the past for community-acquired pneumonia, but some of these other things, antimicrobial therapy in the preceding 90 days, high frequency of antibiotic resistance, and then these other

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risk factors of nursing home or extended care facility, residents' home infusion therapy, chronic dialysis, and a family member with multi-drug resistant pathogens.

I have to say, I think we got it wrong. We are now redoing the HAP/CAP/VAP guidelines that's just being started by the IDSA and ATS, and we welcome the FDA to have input into that to help with this clinical trial design, because in fact some of these don't make a lot of difference.

If you had antimicrobial therapy in the preceding 90 days, it may mean you have pen- resistant or macrolide-resistant strep pneumo, but does it really mean you have to cover for pseudomonas and MRSA or acinetobacter? We don't think so.

Same thing even for this health-care associated pneumonia. There is more and more data that suggests that it's not just where you reside in a nursing home but the degree of disability there. Do they have a

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trach and a PEG, and are they bed-bound? Or are they getting up, feeding themselves, clothing themselves? And if that's true, then they are less likely to have these multi-drug resistant pathogens, and really should be treated more like community-acquired pneumonia, and in fact, we've had some disasters reported when we treat those patients like hospital-acquired pneumonia.

And these last three are really risk factors for MRSA, but do we need to cover for pseudomonas or acinetobacter? So I think there is going to be some re-entrenchment and revision of these risk factors in pulling some of these patients out of the HCAP and HAP guidelines and pulling them back into the community-acquired pneumonia guidelines.

But I think we need to be very aware from a safety issue of excluding these patients that meet the true risk factors for multi-drug resistant pathogens.

Now one of the other things that

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we felt strongly about is that the comparator drug ought to be consistent with IDSA ATS CAP guidelines, and this has something to do with the issue of constancy and clinical relevance for sure.

This is our set of guidelines for hospitalized community-acquired pneumonia. In the large bold is the newer fluoroquinolones and cephalosporin plus macrolide. We kind of, in the text said, for carefully selected patients, azthromycin alone, and in even smaller print, substituting doxyxycline for a marcrolide, because we don't have the evidence base to support some of those.

This is actually clinical trials that suggested that it's good, and that it could be used. But the concerns about resistance are one of the things that are driving our deemphasizing that recommendation from even guidelines published four to five years earlier.

So we think that in order to help

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with this constancy principle, that you need to use what is the most current comparator types of drugs for these clinical trials.

Now we were looking mainly at data such as this, that comes from 14,000 patients looking at mortality here. This is adjusted mortality, and it's comparing a baseline of a third-generation cephalosporin alone. Here is a second- or third-generation cephalosporin plus a macrolide or a fluoroquinalone, and you have a survival advantage there that we thought was important and why we felt that we should be recommending these kinds of primary treatment for our patients.

Now in contrast, a different Beta-lactam other than a cephalosporin plus a macrolide had a significant difference in mortality, and so we were saying, we shouldn't be using those kinds of medicines. And we are suggesting to the FDA that you shouldn't be using that as your comparator drugs; that we should be using current up-to-date, modern

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kinds of medicine.

So what the strong recommendation from the ATS and ACCP is that we need to parallel the CMS and joint commission standards to allow American physicians to participate in these trials.

We have a large concern that, with the way that some of these clinical trials are being designed, it's driving the trials to situations where American physicians cannot participate.

You have to realize that the CMS Joint Commission standards drive a tremendous amount of the care for community-acquired pneumonia, and there are important issues that have to do with enrolling patients.

We have a very difficult time getting IRB approval if they aren't consistent with the ATS IDSA guidelines, which is essentially what CMS and the Joint Commission have adopted.

It's easier to get participants to

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agree to enrollment: not just the patients, but also physicians. We have physicians who will refuse to in fact do studies, and I will refuse to do a study based on what the comparator drug is, if it's not a standard comparator drug that I feel comfortable giving my patient, I won't do the trial.

And I think that one of the things that we need to emphasize that goes to this issue of, is there a benefit to antibiotics, and is there this constancy principle, is that, if you look at community-acquired pneumonia process of care improvement projects have consistently documented that increased adherence to the IDSA ATS guideline recommended therapy is associated with lower mortality.

We can't pull back from that. We can't use clinical trials that don't do that kind of thing.

Newer agents probably will demonstrate superiority to penicillin for

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community-acquired pneumonia. If you set up a clinical trial against penicillin, I'm virtually sure that you will show superiority, if that's what you want to do. But it's not clinically relevant, and I can tell you if making these guidelines we'll never know what to do with that drug, because it's not compared to a drug that we think is going to be at all relevant in that population.

So I think that we strongly recommend consistency with the guidelines. There are some practical implication to that.

We would also agree with previous IDSA recommendations that we could not support placebo-controlled trials. I think that that just - would never pass our IRBs, would never get clinicians to enroll.

You should allow enrollment of patients who have already received an initial dose of a once-a-day antibiotic, such as ceftriaxone.

We are probably going to hear

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later about some of the issues with that, but if you take this away with the CMS emphasis on time to first antibiotic dose, you will get no enrollment in clinical trials in the United States, because we are so driven by that whole issue. We are over-driven to the point of using excess antibiotics.

But if you take this possibility away, you are going to skew the whole study to patients who are not accurately diagnosed at the front end.

If they are accurately diagnosed at the front end, they are getting their antibiotic as soon as possible.

I think you are going to need to allow combination therapy for drugs that may not have a typical coverage. The diagnostic issues are difficult enough, especially for the atypical pathogens, that that is going to be a severe limitation.

We have combinations. We have a cephalosporin macrolide if the new drug has no

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activity against atypicals -- that macrolide will allow comparison to the more standard.

I think one of the other things that came up in here that will help with this whole issue of, is there a benefit compared to placebo, is there a true benefit of this, is looking at shorter duration of therapy.

We do know that patients will survive pneumonia without antibiotics. We know that that is true. That is even true of pneumococcal disease.

But part of the issue is that, if you make your duration of treatment 14 days, then you lose all of that potential benefit in effect, and the guidelines are really pushing toward shorter and shorter antibiotic courses.

Part of this has actually been driven by industry-sponsored trials, and we applaud that, but recommend that we continue to do that, and that going longer will disguise any differences between the drugs.

And I think that disconnecting

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approval for community-acquired pneumonia from linkage to nosocomial pneumonia would probably be of some benefit.

That being said, we also have some concerns about mortality as an endpoint. And what I want to say is that it is unclear that antibiotics will differentially affect mortality; that one antibiotic versus another. This is simply looking at U.S. data on pneumonia and influenza. We have data going back to 1900. The definition has changed a little bit at each of these bars here, but what you can see is that there is a very - and this is a log scale - so when penicillin first became available, we saw a nice, fairly gratifying drop in mortality, and then this plateau-ing.

Now this actually illustrates several things that I think are pertinent to this whole discussion.

This is a huge drop. This is a log scale, this is something that shows that

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there are clearly antibiotic effects, and that there is clearly a benefit, and is strong evidence against any type of placebo-controlled trial.

On the other hand we are not seeing a significant difference in mortality that has come since that time, suggesting that the constancy principle is actually in play here, that in fact we have not been able to show one drug is better than another drug as far as mortality. Mostly what we have been doing in this period of time is fighting a rearguard action against the development of resistance, first resistance of staph to penicillin, since staph has been a player all along -- the availability of atypical coverage in this area as was just mentioned.

But at this time we're really fighting a rearguard action against the development of resistance. And that's why I say, you could do penicillin as your comparator drug, and the new drugs would

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probably be superior, but it would not be clinically relevant.

And as I say, it's unclear that antibiotics will differentially affect mortality. Most of the time I wear a hat as an intensivist, and we talk about immunomodulatory therapy as being the thing that may affect mortality there.

If you talk about moderate community-acquired pneumonia, in our definition that being patients who are not admitted to the ICU but admitted to the floor, it's unclear that pneumonia is the greatest risk for death, and in fact it may be cardiovascular. If you talk about mild community-acquired pneumonia, the death rate is so low it's really bad luck. It's, they got hit by a car, most of the time, and that's the leading causes of death in those types of patients.

This is actually Dr. Musher's data looking at pneumococcal pneumonia and acute

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cardiac events. And the bottom line is about one out of five patients, 20 percent, have an acute, new cardiovascular event while admitted for the prototypical community-acquired pneumonia.

And there is a lot of data that is starting to accumulate that, in fact, infection and accelerated cardiovascular disease are actually not disconnected but are intimately related. And what you can see is, there is a big difference in mortality that occurs in those patients compared to the others.

So to say antibiotics are going to make a difference in cardiovascular mortality is a stretch. It may be true, but we haven't proven that yet.

If you actually look at severe community-acquired pneumonia in patients who die at age less than 55, and I emphasize age less than 55 - we all know that this is a disease where mortality goes up in the elderly

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- but if it's age less than 55 you get rid of a lot of the issues of comorbidity. You get rid of the issue of palliative care in patients who are admitted with pneumonia, which is a very big issue in the elderly patient.

A large number of admissions in a Canadian province looking at the overall incidence of these things, the incidence in patients who died in the first 11 days versus all deaths. And what you see are these types of things that get patients into the intensive care unit - acute respiratory failure, respiratory arrest, the need for mechanical ventilation, or shock - occur in a very small minority of patients, and yet, in a fairly high percentage of patients that actually die. So that's why, if you are going to use a mortality endpoint, you have to use these kinds of patients; you have to go to the intensive care units.

The flip side is, 50 percent of

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the deaths never made it into the intensive care unit, so there are deaths that occur on the floor. We need to be cognizant of those.

And basically what Im saying is, if you look at lethal pneumonia, there are some that have septic shock and die of it, and pneumonia is one of the most common causes of septic shock. There are patients who die of respiratory failure, of ARDS, and pneumonia is the leading cause of ADRS in a non-trauma population.

But there is this group of patients who don't fit into either of those buckets that actually die. So and we don't understand those very well, so it's unclear that antibiotics are going to make a difference.

Now the exception is inappropriate initial empiric antibiotics in severe CAP. We've got several studies, including studies of immunomodulatory agents that say, okay, if you have inappropriate initial antibiotics,

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there is an excess mortality and severe CAP.

The problem is, we don't know which regimens are going to lead to the greatest instance of appropriate initial therapy, because that group has never been studied. And that goes back to our plea that you actually include those in clinical trials here.

Now I say all that to say it's unclear that antibiotics will affect mortality, but if you go back to this thing that I just showed you here, this is a mortality graph. There is a difference here between third-generation cephalosporins and third-generation cephalosporins plus a macrolide or a quinolone. There is a definite mortality of about 2 percent there that we felt was important enough that it's statistically significant when you use the 14,000 patients there.

So there does seem to be some difference. There is an even wider

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difference. Here is almost a 10 percent difference between a Beta-lactam macrolide versus a specific type of Beta-lactam cephalosporin macrolide. And so there is a difference in mortality based on antibiotic treatment.

We don't want to lose this benefit that we are trying to achieve here. So it goes back to this idea of, you need to compare it to the modern standards, and we don't want you to go back to comparing to these kinds of drugs, because this is the mortality benefit we want to preserve.

This is another study looking at - the study was purportedly to look at atypical coverage for bacteremic community-acquired pneumonia. Now these were bacteremias that not only were pneumococcus, but included gram negatives and a variety of other things.

If you got mono-therapy, it was associated with a lower mortality rate. Most of that mono-therapy was actually a

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fluoroquinalone. If you got combination therapy with atypical coverage, there was a trend toward a mortality benefit that was almost completely driven by the macrolide in this particular circumstance.

So once again, the antibiotics you use do have an association with mortality. It just takes the 10,000 to 15,000 patient trials to show that, and those are going to be too big for the pharmaceutical industry.

This is looking at combination therapy, of bacteremic pneumococcal pneumonia; a variety of prospective observational studies, retrospective studies; but a very consistent pattern in all of these that if you add a second drug to a Beta-lactam, usually a cephalosporin, you get a significant survival advantage for bacteremic pneumococcal pneumonia. The only study that didn't show the advantage was a clinical trial of an anti-TNF agent, and this is the placebo group in that particular trial, and it required organ

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failures and shock.

This is a recent study on combination therapy for severe CAP. Now this is patients admitted to the ICU. If the patients didn't have shock there was no difference; but if the patients had shock, antibiotics made a difference.

And so we don't want to lose this benefit as well. And in this study the difference remained even if inappropriate initial therapy or deaths in the initial 48 hours were excluded.

So the conclusion is mortality is an important endpoint. It needs to be in the studies. If you are going to look at a mortality endpoint, you need to include patients who will have a mortality, and that is severe ICU-admitted patients. But we would strongly recommend that it can't be the primary endpoint for sure in superiority trials, because we don't think that there will ever be a large enough trial, a clinical

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trial, an industry-sponsored trial, that would ever show that superiority.

And for non-inferiority trials, the margin should be small, to preserve that benefit we have. And once again, the comparison should be to the current guideline-recommended therapy.

Now what about other endpoints? For moderate CAP the clinically and financially relevant endpoint is hospitalization, how long the patient stays in the hospital. The problem with that endpoint as an endpoint in itself is that hospitalization is often used to correct the other medical issues that occur in patients with community-acquired pneumonia. So 20 percent are going to develop some kind of cardiovascular disease that needs to be addressed, whether it's an arrhythmia or congestive heart failure or diabetes out of control, a variety of other things.

So we would actually favor the use

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of objective criteria, such as time to clinical stability, rather than the subjective kind of clinical criteria, or the use of duration of hospitalization as a simple endpoint.

It also, using time to clinical stability, helps for intravenous-only study medications. You can require intravenous drug up until they reach that point, and then you can either decide to go with a different drug, because you have met your endpoint, or you can not continue with an oral agent afterwards.

And these tools have already been developed, and actually have already been used in some clinical trials.

For mild CAP the clinically relevant endpoint is return to normal activities; that is returning to work for people who are older, returning to school for younger people. So because of that, we would favor the use of patient-reported outcomes.

Patients who are treated as an

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outpatient, it really is a self limited disease; therefore, assessment at a static endpoint time is unlikely to demonstrate differences, and we - for both of these, whether it's time to clinical stability or patient-reported outcomes, these should all be time-based comparisons rather than at a static endpoint, especially two weeks out from beginning of disease. And the margins suggested by the IDSA committee appear to be reasonable and supported by some of the prior literature.

Now I'm just going to end with a couple of comments about what seemed to be a very exciting thing and something that I think will in the future make these trials a little bit more accurate, such as the use of procalcitonin and to suggest that, in fact, this is something that the agency can do within your own agency.

One of the biggest problems we have is that right now procalcitonin is not

FDA-approved for the indication of community-acquired pneumonia, for separating bacterial disease from viral disease; that's not its indication, and you'd be theoretically asking us to do something that you haven't approved.

One agency - part of the agency hasn't approved. And we think that it would be very helpful to have that coordinated.

Procalcitonin may have minimal impact on community-acquired pneumonia; in the studies that were actually presented, it had a major impact on acute exacerbations of COPD, and things like that, but only about 10 percent. And using it as an endpoint, a normal level or drop in level may be supportive evidence of cure, but the implications of a persistently elevated level are less obvious.

The other issue is that, once again the FDA has been a barrier to use of point of care tests, such as the Binax urinary antigen. We get flak from our lab that they

will not do it in the time-dependent kind of manner that we need to involve patients in clinical trials, and the institutions that have been granted a waiver from the clinical lab to do it as a research test on patients are the ones who have been able to actually enroll patients and have a high diagnostic rate for pneumonia in those patients.

So I will just end with a couple of things that are implicit in these statements that are some of the goals that the ATS and ACCP would strongly support.

We think the problem of increasing antibiotic resistance is real, and an anticipatory approach is needed.

The pharmaceutical industry, we agree, needs to have clear guidelines, and also the ability to be more nimble in recruiting patients. And also the majority of these patients should be studied in health care systems that are similar to the United States. And one of the big concerns that we

have is that clinical trial design has actually driven these trials overseas, not to our partners in Europe, who we would find very acceptable, but to South America, to Asia, and to places that have health care systems that don't look like ours do and induce a different kind of risk factor that, as far as the comparability of those trials and the constancy principle, that you would like to have for the U.S.

So thank you for allowing me to make these comments on behalf of the ATS and ACCP. Thank you.

ACTING CHAIR TOWNSEND: Thanks, Dr. Wunderink. If you can stay there for a second. Dr. Cox has told me that, as chairman, I have carte blanche to do whatever I want, and so we have some time for questions if anybody has any for Dr. Wunderink.

DR. SPELLBERG: Rich, thanks for a very nice talk.

I - you and I had talked before -

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I had forgotten to mention during my talk that IDSA's position about the PSI is that it is very important to include as a tool to fill the constancy assumption, but clearly we recognize the limitations of the PSI scoring.

Ironically, the biggest limitation is that it so closely adheres to age that young people almost never get into class IV or V, and I think you highlighted that point. And so the position paper that we put out does say explicitly that the PSI score should be a basis, but there needs to be an allowance in trials to have physiologically accepted markers of severe disease like hypotension, mechanical ventilation, to supersede the PSI score in terms of disease severity. And I wonder if we could get you to comment on that kind of a relationship.

DR. WUNDERLINK: As you know, we'd agreed this - I think the PSI is helpful for comparability, so when you have a trial of, let's say, moderate community-acquired

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pneumonia, that's admitted to the hospital, you can do the PSI scores to say, okay, the patients in the two groups look similar as far as those kinds of scores. It functions probably very well in that way for patients who are not admitted to the ICU.

In the ICU we have other scores that are probably better, like APACHE score or things like that that are a little bit more - that are even more physiologically based. The PSI is somewhat physiologically based, but gives disproportionate weight to age and underlying diseases that may be very stable.

DR. PATTERSON: I just have a clarification on the CAP categories which is on page two of the handout. But you had mild, outpatient, moderate, hospitalized, outside the ICU, and severe ICU admission.

So is your suggestion that the categorization be according to that, like whether they're in the ICU?

DR. WUNDERINK: Yes, that's what

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I'm saying is, clinicians, when you say severe community-acquired pneumonia, they're thinking they ought to be in the intensive care unit. Mild, everybody would accept is outpatient. This category of mild and moderate admitted to the hospital or - trying to parse out who admitted to the hospital is mildly ill versus moderately ill. I don't think clinicians make any difference.

And from a clinical trial design, there is no reason to suspect a different distribution of microorganisms in patients based on PSI intermediate kind of scores, or this previous kind of designations of mild, moderate, both being admitted to the hospital.

DR. PATTERSON: I guess my only concern with that is that certainly in public hospitals in recent years we have these designations, progressive care units. And overall we have much higher acuity level patients than we did a few years ago.

And so we end up putting patients

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in the PCU, progressive care unit, that we ordinarily would have in the ICU. And so, I just - you know, it seems to me that using physiologic markers might be a more objective way, because it might even differ from hospital to hospital who goes into an ICU.

DR. WUNDERINK: Yes, that's a very valid point. And that's why the ATS IGSA guidelines actually have a set of criteria for what we call severe CAP. Some institutions can take even noninvasive ventilation in a high dependency unit outside of an ICU. We would still consider those severe CAP.

So I think there are clear issues of definitions here. But I think what the IDSA TS guidelines would suggest as severe cap come a lot closer to the way clinicians think, than to call severe CAP just somebody with even a PSI IV or V who is admitted outside of one of these high dependency, specialized care kind of units.

DR. PATTERSON: Okay, and then just

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one more question on the treatment outcomes data, which is on page six, in the Gleason study, could you remind me what the Beta-lactam plus macrolides, the non-cephalosporin Beta-lactam was?

DR. WUNDERINK: So they would be penicillin. I'm sorry for all you ID physicians who think that penicillin for - for pen-sensitive strep pneumo, that penicillin is the drug of choice. It was actually penicillins and penicillins with a Beta-lactamase, so it would be unicins, osin, those kinds of medications.

DR. PATTERSON: So Beta-lactamase inhibitors?

DR. WUNDERINK: Yes, they actually ended up in that high mortality category.

DR. MUSHER: There were so many good points really it's a terrific talk. But there are two minor questions I would ask, and actually one deals with the one Dr. Patterson just raised.

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That study was treatment outcomes, but that's - I would imagine it's totally driven by selection bias of the antimicrobial agents.

DR. WUNDERINK: I think that -

DR. MUSHER: We just have to make that very clear.

DR. WUNDERINK: So if you go back to it, or if you look at that -- and immunoglycoside is associated with excess mortality.

DR. MUSHER: Sure. If you add the immunoglycoside, the patients do worse and they die.

DR. WUNDERINK: That's the implication, when in fact that's not probably the reality. You add an immunoglycoside when you expect a gram negative. What we don't know is how many of those patients actually had gram negatives, versus did not.

So if they did have a gram negative, that's associated with an excess

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mortality. What would be against that is, we have somewhat downplayed the issue of pseudomonas coverage in severe community-acquired pneumonia. It turns out that there are studies that 50 percent of ICU patients have risk factors for pseudomonas, according to the old ATS guidelines, and therefore would get some of these semi-synthetic penicillins and things that were more oriented that way; they actually do worse than getting a cephalosporin-macrolide combination.

So we are actually backing away from that, trying to be a little bit more definitive about who really does have risk factors for these gram negatives.

So even though I agree with your point that adding in immunoglycoside probably is a selection bias if that's a patient at risk for gram negatives.

The flip side of not treating them with the standard regimen is actually, there is a price to pay.

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DR. MUSHER: Well, that was my first point. I just did want to say that it really - since it's not prospective, it's retrospective review of data, it is very largely dependent upon selection bias.

DR. WUNDERINK: And that goes to my strong recommendation of including severe CAP in prospective trials.

DR. MUSHER: Absolutely. Absolutely. The other point I wanted to ask you, do you think there is enough - there are enough studies to validate the procalcitonin that renders it possible to start making that a standard?

I don't. I think there is one study published. There are a couple at various stages along the way, and I think it's very preliminary, though it's been used for a number of years. And I don't think it should become a standard for us to use.

DR. WUNDERINK: Well, I'm intrigued by the studies.

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DR. MUSHER: Intriguing, yes.

DR. WUNDERINK: I think that you're right, it's only had one study in the Swiss system that showed that you could minimize the use of antibiotics.

Our approach will be to actually use it to say that this patient does not have pneumonia, does not need antibiotics. And so I would say it may be valid to look at it retrospectively to say, okay, this group of patients probably didn't have pneumonia, therefore, an objective way to help out, since we have such a difficult time with micro-diagnosis, especially procalcitonin has its best potential benefit in the mild cases that come to the emergency department but don't get admitted, or maybe the ones that are admitted but for sure not to the ICU.

And in that setting, viral diseases is a clearer issue. So it may help in those types of studies.

DR. WUNDERINK: But it still is

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based largely on a single published study so far?

DR. MUSHER: Right. So it needs to have a lot of confirmation before we start using it?

DR. WUNDERINK: Yes.

ACTING CHAIR TOWNSEND: Thanks very much, Dr. Wunderink. We'll move along.

The next presentation will be from Dr. Robert Nelson, on ethical considerations for trials of CAP; and Dr. Sarah Goldkind.

ETHICAL CONSIDERATIONS FOR TRIALS OF CAP

DR. NELSON: Thank you.

Before starting, as I present the thinking that Sarah and I put together about ethical considerations, I'd just like to give you some clinical background on both of us, so that our ethicist background is not the only thing that you recognize as our expertise here.

Sarah is a general internist, and

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my area is pediatric critical care, having practiced that for about 20 years before taking this position.

Now clearly, we've heard the need for many unmet needs. CAP is the sixth leading cause of death in the United States, and the number one cause of death from infectious disease; we've heard that clearly presented.

And there are certainly a number of cases that occur, rendering CAP an important public health issue. And with a differential mortality, as again we've heard with 80 percent of those treated with CAP as outpatients having a low mortality, which increases as you, then, are hospitalized and move toward ICU admission.

Now since I'm a pediatrician I felt it's important to put the issue of CAP and pediatrics into a broader perspective.

Pneumonia is the leading killer of children worldwide, and you should notice that

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it's the leading killer, even if you combine measles, trauma, and AIDS together -- with over 2 million deaths per year.

Most of this occurs in the developing world. As you'll notice there is a considerable difference between developing countries of 20 percent and the industrialized world of 2 percent, and Sarah will give some further reflections in the adult experience about generalizability in those two areas, particularly noting the final point on that last slide from our prior presentation.

So this is the outline of our discussion. I'm going to present thoughts on what I'll call the two ethical requirements that we need to meet, the ethical requirement of scientific validity, which is a large part of our discussion over these two days, focusing on choice of control group, assay sensitivity, noninferiority/superiority designs. Again, conceptually, there will be plenty of discussion from the statisticians

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and the trial design people about how to go about doing that.

The second requirement is the ethical balance of risk and benefit, and the issues surrounding withholding known effective treatment, withholding antibiotics in this case.

Sarah will then address some design modification and other issues in adult trials for community-acquired pneumonia, and then I'll return for some final thoughts on pediatric studies, and then the conclusion.

Well, clearly the choice of control group is an important issue. It's a critical decision affecting a whole range of issues, the inferences you can draw, the ethical acceptability of the trial, minimizing bias, the subjects and the recruitment that you would have, the endpoints, the credibility of the results, acceptability to regulatory authorities, and other features of the study, conduct and interpretation.

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This is a big issue in the design of trials. It's also key to the inferences that you can draw, and particularly key to the causal inferences, because it allows you to discriminate patient outcomes that are caused by the test treatment from outcomes caused by other factors such as the natural progression of the disease, observer or patient expectations, or other treatments.

Now there are a range of type of control groups. You heard presentations involving both concurrent controls, and then external or historical controls regardless of treatment. Now usually the standard would be a concurrent control, where you choose the control and the test group from the same population, usually by randomization and treated concurrently.

Now there are four types that are identified in ICHE-10, choice of control group. And I'm going to focus primarily on placebo and active controls, but have a couple

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of comments on dose response and historical controls as we go forward.

So external or nonconcurrent control group obviously raises serious concerns about the ability of trials using such a control, regardless of the comparative treatment to ensure comparability of the test and control groups, and to minimize important biases.

This often has less to do with the exact drug that they may or may not have gotten, but all of the other treatments that are provided, including intensive care and other sort of hospital treatments that have been proved over the years to minimize the comorbidities that may come about with hospitalization.

And I would suggest that going forward that I hope this is uncontroversial that this would not be an acceptable trial design for a study of community-acquired pneumonia.

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Now the other design that is offered in ICHE-10 is a dose-response design. And if you look in the literature, you may well see many antibiotic trials which compare two regimens, often a short course or a long treatment course, which can use either a superiority design or a noninferiority design. And thus I would suggest to you that a dose-response design raises some of the same issues as an active control design in terms of whether you choose a superiority or a noninferiority design.

Now of course the choice of the lower dose or the shorter course must be a fair comparison since the trial conditions should not favor one treatment over the other, or what might often be called a sort of hidden placebo; you pick a dose low enough that you know is not going to be effective, thinking people won't notice. That's not really a good design, and raises those same issues as placebo controls.

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So the intent here is to say, where we really need to focus our attention is the choice of either an active control or a placebo control. And there are two approaches regardless of which control you pick to establish efficacy, although obviously we generally don't want a drug that is simply noninferior to placebo.

The superiority of test treatment to control, whether you pick placebo or active, and then the similarity of the test treatment to a known effective treatment or active control, picking one of either two designs, equivalence, equally effective, or noninferiority, meaning it's not less effective by a margin that you pick.

Now the key assumption here as we've heard and was presented is that the active control is effective under those trial conditions which is referred to as the notion of assay sensitivity.

This is the definition. The

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ability of a clinical trial to distinguish effective treatment from less effective or ineffective treatment. And it's pointed out in ICHE-10 this has different implications for whether you have a superiority or noninferiority design, and this will go to somewhat of what has been put on the table already about this constancy assumption.

So assay sensitivity for a superiority trial, if in fact that trial lacks sensitivity, the trial will fail to show that the new drug is effective compared to the comparator. If it's a successful trial, by definition, you have assay sensitivity, thus leading to the notion of a superiority trial being a much more useful design.

In a noninferiority trial, if it lacks assay sensitivity, and we'll expand on that a little bit, the trial may find that ineffective treatment to be noninferior, even to a drug which under those conditions is shown not to be effective given the trial

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design.

Now you've heard in prior presentations that this assay sensitivity in a noninferiority trial depends on two determinations. The first is historical evidence of sensitivity to drug effects, where you have similarity of designs. Past trials are regularly able to distinguish effective from less effective or ineffective treatments.

And the second is appropriate trial conduct. Now you've heard the term constancy assumption. The question I want to put before you at some point for discussion is, appropriate trial design is more than simply a stratification. Appropriate trial design -- if you don't have appropriate trial design, you may undermine the ability to distinguish effective from less effective or ineffective treatments, based on the conduct of the design, the conduct of the trial, regardless of whether or not you have chosen a stratification design.

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So that's an important issue in the selection of noninferiority designs.

Now the historical evidence of sensitivity to drug effect has to be evaluated before the beginning of the trial. A lot of the discussion today and tomorrow is going to be focused around that. And it's based on the notion of having appropriately designed or conducted trials, using a specific treatment or other treatments with similar effects.

You heard, if you will, the domino theory of the ability to compare across trials, and whether you find that compelling into the modern era, as opposed to using a comparator back in earlier trials was raised in the prior presentations.

And without well supported historical evidence, the demonstration of efficacy using noninferiority trial designs is not possible and should not be attempted. This is a quote from ICHE-10.

You are going to have a lot of

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discussion going forward by people more qualified than I am about the selection of a noninferiority margin. You've seen this definition in the prior presentation so I won't belabor it. I'll just point out that it's only possible if you see this historical evidence, and it actually requires a measure of superiority against a control and not uncontrolled measures.

But the second aspect is appropriate trial design and conduct. And the difficulty here is that this can only be fully evaluated after the trial has been completed. So the planned noninferior trial must share critical design characteristics with the historical trials used to determine that evidence of sensitivity to drug effects exist. This is a point that would need to be discussed - how similar, how not. I would suggest that this is more perhaps than just the stratification of the severity of the patients.

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But the second point is that the actual conduct of the trial needs to adhere closely to those trials that have been used, and should be of high quality, meaning good compliance and few losses to follow-up.

And one of the difficulties in a noninferiority design is that sloppy trial conduct can undermine the ability of that trial to, in fact, distinguish the two, and could potentially lead to an erroneous conclusion of efficacy, unless you have some other way of evaluating the appropriateness of that trial conduct.

So errors that diminish the observed treatment differences, poor compliance, a high placebo response, concomitant treatment, mis-classification of outcomes, undermine the ability of this trial to show assay sensitivity.

There are some errors that in fact may decrease the likelihood of a successful trial. So it's not all trial conduct issues

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that would undermine a noninferiority trial, but some, and unfortunately, there are many trials that are conducted that have issues with each one of these particular aspects.

So in terms of the conduct of a noninferiority trial, you need to review it to see if there are factors that might obscure differences between treatments, such as differences in the populations enrolled, hopefully eliminated through good randomization; use of concomitant therapies, hopefully constrained by appropriate trial design; compliance with therapy extent and reasons for subjects dropping out -- a lot of issues that would have to be looked at.

There are some - and those that might make the trial different, such as atypical outcomes with active control treatment. So for example, if you see an unusual difference based on your historical trials of the response to that active control, could you assume then, that the trial did or

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did not have assay sensitivity?

And concurrent trial monitoring may be necessary to both minimize risk to subjects and assure adequate trial conduct.

Note I said, concurrent trial monitoring, not retrospective trial monitoring.

So, given these problems with noninferiority designs, what not an active control superiority design? That's been asked by a number of speakers - asked in order to discard that. But let me at least offer a couple of reflections.

In spite of the questions about specifying a reliable treatment effect based on past experience, antibiotics are generally highly effective; you've seen that data.

Thus, a superiority design may require a larger sample size than a non-inferiority trial, depending on the margin. You heard one number thrown out of 10-15,000 in the prior presentation based on the

difference between those two survivor groups if mortality certainly is the endpoint.

The other point is that there may be other advantages of new, over existing, antibiotics that are not captured by an actively controlled superiority study to establish efficacy.

Different resistance profiles, improved safety, ease of administration, formulation advantages, et cetera. In other words, a drug could easily lose on efficacy but still have some of these other advantages if in fact it was not shown to be inferior to the comparator.

What about the ethical preference for active control trial designs? Well, as has been pointed out, there are certainly fewer ethical problems in a placebo-controlled trial because all subjects are receiving active treatment.

I should point out though, that subjects that are on the new treatment are not

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receiving the known effective treatment, so you still have to have a fairly good assumption that in fact they are not receiving an ineffective or harmful drug. So that argument doesn't get you entirely off the hook relative to those that are not receiving the known effective treatment.

If the active control therapy improves survival or decreases irreversible morbidity, withholding of such treatment from the experimental group raises the same concerns that render placebo controls unacceptable.

So again it depends on the evidence you may have as well for that active control.

Now a placebo control, or for that matter, a superiority design, even if you had an active control, may assure assay sensitivity, but can it meet ethical guidelines?

A placebo-controlled trial for

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efficacy is as free of assumptions and reliances on external information as possible, so assay sensitivity is met.

Most problems in the design or conduct of placebo-controlled trials increase the likelihood of failure, as I pointed out. So the trial contains built-in incentives for excellence in trial design and conduct.

And when the primary purpose of a trial is comparison of two active agents, the addition of a placebo control provides an internal standard that enhances inferences that can be drawn. You heard one of those trials mentioned in an earlier presentation as a three-armed trial. The difficulty there is, all you've done is take the ethical concerns about placebo and reduced it from 50 percent of the population to 33 percent of the population. So you still have to address the issues of placebo, regardless of whether you include it in a three-arm design.

So what are some of those ethical

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issues with placebo controls? And this is the recommendations that come out of ICHE-10. When an available treatment is known to prevent serious harm such as death or irreversible morbidity, it is generally inappropriate to use a placebo control.

There are exceptions however, such as when standard therapy has such severe toxicity that many patients refuse to receive it.

When a new treatment is tested for a condition for which no effective treatment is known, there is usually no ethical problem with a study comparing the new treatment to placebo. I don't think that's the issue here today.

When there is no serious harm, it is generally considered ethical to ask patients to participate in a placebo-controlled trial even if they may experience discomfort, assuming adequate informed and voluntary consent.

The question is, can a randomized placebo-controlled trial for community-acquired pneumonia in adult and pediatric patients meet this standard.

Now I'm going to skip over this. This happens to show you the flow chart that's at the end of ICHE-10. It's in the handout, but you can go to ICHE-10 and see it for yourself.

Now this debate over placebo controls has waged over the last two decades. This is a quote from the 2000 version of the World Medical Association Declaration of Helsinki, paragraph 29, which states that the benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic and therapeutic methods. This does not exclude the use of placebo or no treatment in studies where no proven, prophylactic, diagnostic or therapeutic method exists.

Now in 2002 the World Medical

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Association added a note of clarification to this particular paragraph, and the following two slides give you that clarification.

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial, and that, in general, this methodology should only be used in the absence of existing proven therapy.

However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available under the following circumstances.

The two circumstances that they give are, first, where for compelling and scientifically sound methodological reasons, its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method. Read, to assure assay sensitivity.

Or, and I'll return to that small word in a second, where a prophylactic,

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diagnostic or therapeutic method is being investigated for a minor condition, and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

As we go to ICHE-10 this or becomes an and, and that's not an insignificant change, and the World Medical Association is in the process of revising that. Because with this or, this would imply that assay sensitivity could trump the issue of minor serious - avoiding serious harm. And if you change this to an and it would say that you still have to have both those characteristics.

So this goes back to ICHE-10, so again, as a general rule, research subjects should receive established, effective intervention.

There are some circumstances where it may be ethically acceptable to use an alternative comparator such as placebo or no

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treatment. And these are the examples from ICHE-10: a placebo may be used where there is no established effective intervention - again not what we're discussing in this context, when withholding an established effective intervention would expose subjects to at most temporary discomfort or delay in relief of symptoms; or the third would be when the use of an established, effective intervention as comparator would not yield scientifically reliable results, and - not or - and the use of placebo would not add any risk of serious or irreversible harm to the subjects.

So in other words, a placebo-controlled trial for CAP may be ethical if, and only if, the use of placebo would not add any risk of serious or irreversible harm to the subjects.

Now there are some design modifications that are proposed by ICHE-10 where you could add additional control groups, a three-armed trial, additional doses,

factorial designs, other modifications of study design, add-on studies, et cetera, early escape. Perhaps, except maybe for a limited placebo period it would appear that these different modifications may be of limited application to antibiotic trials.

And with that, I'll turn it over to my colleague, Sarah, who will talk about adult studies of antibiotics for community-acquired pneumonia.

DR. GOLDKIND: In the next several slides, what I'd like to do is to focus in on the adult population, and to raise some issues that address how we might minimize risks to the enrolled subjects, yet still continue to maximize scientific validity.

And as I go through these slides, I think you'll see that there is an interplay between these two ethically - these two ethical requirements. And so what I'm going to ask is, how can these two goals best be achieved.

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Can tailoring the study population with more rigorous entry criteria help to improve scientific validity, and also to minimize risks by excluding those subjects who might be more seriously ill? Or would this actually, in effect, limit the generalizability of the results that are achieved from the study?

So these are a few factors that I'm going to discuss as we go through these next few slides.

So in the next couple of slides, what I wanted to capture is what you already know in essence, that people who get community-acquired pneumonia are actually part of a very heterogeneous population, and that there are many different factors beyond just the organism, and the antibiotic that affect outcome.

Being old, as we've heard before, increases severity of the course of illness and mortality, smoking, outpatient versus

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inpatient, and then drilling that down towards versus ICU, USA versus outside the US, other comorbidities and the functional status of the patient when he or she acquires the pneumonia, as well as the virulence of the infectious organism and the antibiotic resistance profile of that organism in that locale.

Community-acquired pneumonia is also affected by how you make the diagnosis, and what's the rigor that's used in making that diagnosis. In limited circumstances, it might simply be made on a clinical presentation and treated empirically. Usually it's made on a clinical presentation coupled with radiographic findings, and treated empirically.

But the empiric treatment is influenced by standard fo care for that region, and the antibiotic-resistant profile for that region; prevalence of resistant organisms and other associated complexities, such as what's the supportive care in that

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region, et cetera.

And what is the ability in that region to make the diagnosis in a definitive sort of way.

So how might we take some of this information and use it to minimize risk? The primary imperative is to minimize research-related risks to the subjects, but without compromising the reliability of the research results.

So could we actually enroll a less sick study population, or a study population that has access to health care including ongoing monitoring to help reduce risks?

And sort of undergirding my comments is this notion that clinical trials - and this was alluded to before - are becoming increasingly globalized. And so, as I talk about what is access to health care, and how are diagnoses made, whether they are made in a pathogen-directed manner, this notion of what is the standard of care in that locale

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undergirds those comments as well, and will undergird the ability to generalize some of the results.

So in looking at the minimization of risk, if a less sick study population is selected, can the onset of antibiotic treatment be delayed to mimic placebo-controlled trial?

We've heard a number of speakers state that they think placebo-controlled trials should not be used on ethical grounds, and the question that I would ask is then, can you actually delay treatment for a short period of time, in essence accumulate some information paralleling the placebo-controlled trial, and not incur additional risks to the study subjects?

So in looking at that question there are two other - there are a few other factors that I think we need to consider, and that is, will this choice of study population provide useful information, provide a

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meaningful endpoint, in light of the placebo-controlled trials that were already discussed that have been done on young, low-risk clinically stable outpatients with mild community-acquired pneumonia. And those were discussed by Dr. Spellberg earlier.

Is that going to add meaningful information to this general background of clinical trial results that we already have?

And then some data demonstrate that antibiotic administration within eight hours of hospital arrival is associated with a significantly lower 30-day mortality and length of hospital stay in both adjusted and unadjusted for patient risk status analyses. And for those who did not receive prehospital antibiotics, four hours was associated with decreased mortality and length of hospital stay. And some of you may be familiar with these results that were retrospectively accumulated on Medicare databases.

But the question that I think they

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lead to is, can a delay in treatment in fact actually be ethically justified?

And although there are -- and another question we can ask is, and I think we've heard repeatedly that prognostic scoring systems do not account reliably or definitively for all factors contributing to mortality. And may not be an effective tool of weeding out that population that would be at higher risk, and therefore, may not be an effective tool for minimizing risk to study subjects.

So now turning to this notion of scientific validity, would it be possible to actually enrich the study population with responders to, for example, subjects who meet the criteria for a pathogen-directed therapy? And so in trying to answer that question, I have two sets of data that are provided by ATS guidelines, and IDSA/ATS guidelines.

And the first states that the only randomized controlled trial of diagnostic

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strategy in CAP demonstrated no statistically significant differences in mortality or rate of length of hospital stay between patients receiving pathogen-directed therapy, and patients receiving empirical therapy.

So that's a point that you all may wish to discuss further.

And then even when extensive diagnostic testing is used, positive pathogens cannot be identified in up to 50 percent of cases.

So given the low virulence of atypical and viral pathogens, and effectiveness of approved antibiotics, will studying mild to moderate CAP give reliable results?

As we think of generalizing the results, we have to think about, number one, what is the intended use population that we are actually preparing and designing the clinical trial for, and also, we have to think about issues related to variations in standard

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of care giving developed countries, U.S., Dr. Wunderink referred to countries that have health care systems that are similar to those in the U.S.

And also the notion of trying to globalize some of the information that we acquire to other countries with other types of health care systems, monitoring systems, hospital settings, et cetera. And part of that relates as well to differing and prevalence of bacterial pathogens including resistant organisms, and nuanced approaches to CAP.

So for example in the United States outpatient empiric therapy might be addressed more broadly, and in European communities it might be addressed more related to a focus on strep pneumoniae.

And now Skip's going to talk about some issues that relate to the pediatric population.

DR. NELSON: Thank you, Sarah.

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I might start by saying that all of the issues that Sarah points out in adult trials pertain to pediatric trials, even if the scientific data behind how you might parse out those issues would apply.

So what I'd like to do is place another issue on the table, and that is the issue of the international impact of this area of trial design.

Here is the classification of World Health Organization, where basically it is by necessity a clinical classification, lacking bedside diagnostic tools and often chest X-ray, define from pneumonia, severe pneumonia, and very severe pneumonia, which to some extent, although I haven't reviewed the guidelines that were suggested earlier might be outpatient hospitalized and ICU, even in the absence of an ICU.

Now the burden of disease around the world is significant in the developing world. Fifteen countries account for three-

quarters of the cases of childhood pneumonia. We are talking 113 million, as opposed to 5.6, and as you can see, India, China, Nigeria, through Asia, South America, Egypt, et cetera.

So apart from the issue of generalizability, from these environments to the United States, which I think is an important question, my point here is just to have us be cognizant of the broader implications of the decisions around trial design.

Now some of the interesting trial designs in the literature in this arena, here's one of three-day versus five-day treatment with amoxicillin for nonsevere pneumonia, meaning outpatient pneumonia. And this was done as a randomized double-blind placebo controlled study which effectively found that there was in fact no difference. And this was designed as an active control equivalence design.

Now here's another one. You

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notice it's moving from outpatient now to inpatient, if you will, severe pneumonia. Chloramphenicol versus ampicillin plus gentamicin for community-acquired very severe pneumonia in children between two and 59 months of age, in low resource settings. It was conducted primarily I believe as you can see here in Bangladesh, Equador, India, Mexico, Pakistan, Yemen and Zambia.

Interestingly enough, in looking at some of the recent trials for antibiotics we would use, these were also the trial sites of many of those antibiotics relative to the prior presentation.

Now one might point out that at the time this was started, chloramphenicol was the World Health Organization recommendation for first line treatment for this condition. And now their recommendation is based largely on this study is that ampicillin and gentamicin should be the first line treatment for community-acquired pneumonia.

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And this was done as a superiority trial. One could argue -- well, I mean we would have expected to see that, but it was designed as a superiority trial.

An important issue, though, is there are limitations of the study. It's a non-blinded design, it could have introduced bias. The point is, though, it was a superiority design, so that issue of bias is a little less concerning I would propose than it would be if it was an active control, either inferiority or equivalence design.

Now the other issue in terms of community-acquired pneumonia in developing countries is just getting the antibiotics to them at all. And it turns out there is a fair dropout in terms of hospital referrals, if you live anywhere from 40 to 150 miles from the nearest hospital, you won't get there.

And of 27 countries based on data from I think 1999 and earlier, only 19 percent of children under five with pneumonia actually

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received any antibiotic, leading to a trial which looked at a short course high dose oral amoxicillin, which you could actually bring with you when you were visiting the villages, compared to hospitalization with basically -- here we go, ampicillin followed by oral amoxicillin for inpatient hospitalization.

This again was done as a equivalence trial showing equivalence. It did raise some issues about study design, because they chose not to blind it, given the issues of trying to randomize and give placebo injections. So it was an unblinded study, but nonetheless it's leading to policy recommendations that antibiotics be given at the time of diagnosis based on clinical signs when the health care worker is visiting the child where they live and not just relying on referral, which could often be miles and miles away and never actually happen.

Now I would suggest, without giving you all of the documentation to support

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this, that there is wide agreement on the ethical principles for the conduct of pediatric research worldwide, and that agreement basically is that either the research must present a balance of risks and potential benefits comparable to the available alternatives; or if that is not the case be restricted to either minimal or low risk absent direct benefit.

The conclusion in this is that if in fact you make a decision to withhold known effective therapy from children, one would have to argue then that that withholding, which obviously doesn't offer direct benefit to that group of children, would have to present no more than a minor increase over minimal risk, which is the language taken from 5053, and I would suggest to you that that would be pretty much the same standard as this no-evidence-of-serious-harm, either morbidity or mortality, that I presented to you in the ICHE-10 document, so that those two documents

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I think are in harmony, depending on how you interpret minimal risk.

So the ethical standard for choice of control group in CAP and clinical trials to begin to conclude, there are concerns that the use of an established effective intervention as the comparator in a noninferiority margin design would not yield scientifically reliable results, lending credence to the need for either active superiority or placebo controlled trial designs.

The scientific ability to set a credible noninferiority margin is key to the resolution of this discussion.

A placebo controlled trial for CAP would only be ethical if the use of a placebo would not add any risk of serious or irreversible harm to the subjects.

There are doubts that a CAP trial could be designed to meet this standard.

A cautionary note, and this is a quote from ICHE-10, where a placebo-controlled

trial is unethical, and an active controlled trial would not be credible, it may be very difficult to study new drugs at all. I'm not suggesting that as a conclusion; I'm just pointing that out as a cautionary note.

So what is the challenge? If you are looking at an active control trial, the challenge is to assure scientific validity with either selection of appropriate noninferiority margin combined with meticulous trial conduct, using a noninferiority design, or the use of a superiority design.

If you are looking at a placebo controlled trial you need to assure the ethical treatment of subjects by avoiding any risk of serious or irreversible harm. All trials must meet these two dual ethical requirements of either -- of scientific validity, and a second and appropriate balance of risk and potential benefit.

Now this is the dilemma that you are going to be faced with. And as Odysseus

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trying to make it between Scylla and Charybdis, of these two rocks the one reaches its heaven in its peak is lost in a dark cloud. There Scylla sits, the dreadful monster of withholding known and effective treatment.

Down here is Charybdis, the whirlpool you may sink to. Three times a day she vomits forth her waters, and three times she sucks them down again.

See that you not be there. The Charybdis of lack of scientific validity or of assay sensitivity.

And of course Odysseus basically responded, is there no way of escaping Charybdis and keeping Scylla off when she is trying to harm my men? And the goddess replies, you daredevil, you will not let yourself be beaten even by the mortals.

I will suggest that is your task. I will remind you that Odysseus lost six men in trying to get through these straits, and so

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you should look around.

(Laughter)

And good luck.

ACTING CHAIR TOWNSEND: Thanks again, Dr. Nelson, Dr. Goldkind.

We do have some time for some questions from the committee members if anybody has any.

Dr. Musher.

DR. MUSHER: An interesting talk, and I'm glad you came around to the conclusions that you did regarding the use of placebo.

I don't understand your comments about the use of historical controls. It seems to me that I couldn't, even in a study, use my own patients from a few years before, my very own patients, I couldn't use them in evaluating some new treatment because unless it's absolutely constant, unless it's randomized, unless it's concurrent, unless it's blinded, I don't think I'd have valid

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results.

So I don't see how an historical control could possibly be used. If you would enlighten me, I would appreciate it.

DR. NELSON: I thought that's what we said.

DR. MUSHER: Okay.

DR. NELSON: I guess maybe I misspoke or left out an important modifier.

DR. MUSHER: If that's your conclusion, I'm delighted. It was very theoretical and highfalutin and fancy sounding and I wasn't sure.

(Laughter.)

So I'm delighted that's what your conclusion is. Thank you.

DR. NELSON: I don't think anybody has that seriously on the table in this arena.

DR. MUSHER: Okay, I'm sorry then if I just plain blew it, I am sorry.

DR. NELSON: But I will point out that the choice of noninferiority margin is

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adjustment based on historical controls, and so that - you are still in that quagmire a little bit.

DR. MUSHER: Of course, of course. The choice at the margins. Thank you very much.

ACTING CHAIR TOWNSEND: Dr. Rex.

DR. REX: Thank you, that was really a fun talk.

I want to put in a comment, something that the last three speakers have almost said, and actually Dr. Wunderink came very close to it but did not really point it out.

The real reason for new antimicrobials is the rising tide of antimicrobial resistance. When it comes to the study of a superiority based approach, you might say, well, let's just study resistant bugs. I want to point out that in any reasonable design the new drug and this feature of it that it's more active is

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eliminated; it receives a handicap.

Because what is the inclusion criteria for the study? A rule that says if the isolate is resistant to the comparator, the patient comes out of the trial. I just want to point that out.

Dr. Wunderink came close to that when he said, we won't study penicillin because it is a meaningless comparator; it doesn't have enough activity. This is a corollary of that. The very feature that we most want in a new drug is the one that we are not permitted to test.

ACTING CHAIR TOWNSEND: Dr. Patterson, did you have a question?

DR. PATTERSON: Yes, I did, for Dr. Nelson. In that placebo trial, what were the microbial etiologies and viral diagnostics used in that?

DR. NELSON: Any of those three studies that I showed you did not have any diagnostics. They were all conducted in

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resource poor areas, and so I think one of the issues in bringing -- I'm not suggesting that that is a good trial design for our environment. But I was just trying to broaden our horizon to recognize that comments on trial design would impact also on the interpretation of those studies.

DR. PATTERSON: And then I had a comment on Dr. Goldkind's question about can delayed therapy be justified. I mean hospitals these days are using CMS measures because they get more from Medicare reimbursement if they use that.

And one of the CMS measures that is monitored is early therapy, four to eight hours, for community-acquired pneumonia. So I would just question whether it's justified or not, whether it's really feasible to do that in a U.S. hospital. Because I think most hospitals now are monitoring that as a quality measure.

DR. GOLDKIND: So thank you for

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that comment. I appreciated your comment earlier today, too, which sort of brings us back into the hospital setting where a lot of these trials might have to be conducted.

So yes, I agree.

ACTING CHAIR TOWNSEND: Dr. Dowell.

DR. DOWELL: Thanks. I just wanted to come back to the issue of historical controls, and ask you if you could clarify what seems to be a contradiction; that is, clear agreement that historical controls wouldn't be an acceptable trial design.

And yet how are we -- is it okay then to use historical controls then to determine noninferiority margins?

DR. NELSON: I guess two comments. That inference is part of determining the noninferiority margin. Whether it's okay or not is precisely the task laid before you, and the next presenter in many ways -- I was going to allude that perhaps the statistician could be Odysseus -- but he'll say a lot more about

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how you might try to draw those kinds of conclusions I believe in looking at those slides.

ACTING CHAIR TOWNSEND: Dr. Temple.

DR. TEMPLE: The very first step you take in using an historical control is assessing the past so you can use it as the estimate of the effect in the present study.

So there is an intimate connection between the use of historical experience, even though they are not nominally historical controlled trials, because you do randomized to the present; you do randomizing in the new trial, too, to the active control.

But all the things that E-10 warns about in describing historical controls -- you should take a conservative estimate of the effect, which we do when we think about the margin, we always take the lower bound of a confidence interval and you should try to make sure the new trial study is the same kind of people. All those warnings apply in the

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active control trial.

So the distinction between the two is quite modest.

Can I ask one other thing? Suppose somebody did a trial where you thought maybe the population did have a fair number of people resistant to whatever the current therapy is, but included them nonetheless. That would be a superiority trial. Wouldn't everybody be happy with that? I mean that goes to Dr. Rex's question.

I don't know how you design it that way, and whether it's really ethical to use the active control in that population if you are not so sure it's going to work. But if there were something like that and it were unavoidable, that's a kind of design that might be attractive, because it's very easy to interpret. No?

DR. NELSON: Is that a rhetorical question?

(Laughter.)

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