FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

FRIDAY, NOVEMBER 4, 2011
8:00 a.m. to 3:45 p.m.

Hilton Washington, D.C./Silver Spring
8727 Colesville Road
Silver Spring, Maryland

A Matter of Record
(301) 890-4188
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PROCEEDINGS

(8:00 a.m.)

Call to Order

Introduction of Committee

DR. MOORE: Good morning, everyone. If everyone could please take their seats, we can get started. We've got a full docket today just like yesterday, so I want to use our time efficiently.

I would like to remind everyone present to please silence your cell phones, Blackberrys and other devices, if you have not already done so.

We'll start by going around the table and introducing ourselves. Today we're going to be tackling ventilator-associated bacterial pneumonia/hospital-acquired bacterial pneumonia as part of the FDA's AIDAC meeting.

So let's start on the right with Dr. Rex.

DR. REX: Good morning. My name is John Rex. I'm a board-certified physician in internal medicine and infectious diseases, formerly professor of medicine and infectious diseases at the University of Texas Medical School at Houston.
I'm currently vice president for clinical infection at AstraZeneca Pharmaceuticals.

As Dr. Minh Doan will note, my role in the committee today is that of a non-voting industry representative. In this role, I represent regulated industry as a whole rather than AstraZeneca Pharmaceuticals or any other specific sponsors.

In addition, I am also currently the chair of the Consensus Committee on Microbiology for the Clinical Laboratory Standards Institute, also known as CLSI, an international consensus organization that develops methods for testing and interpretation of microbiology data. I will also comment from that perspective today as such issues become relevant.

Thank you.

DR. SHYR: Good morning. My name is Yu Shyr. I am the director of Center for Quantitative Sciences at the Vanderbilt University. I'm also the professor of biostatistics, bioinformatics, and preventive medicine.
DR. CALHOUN: Good morning. I'm Bill Calhoun. I'm a professor of medicine and vice chairman for research at the University of Texas Medical Branch in Galveston.

DR. WIEDERMANN: Good morning. I'm Bud Wiedermann. I practice pediatric infectious diseases at Children's National Medical Center in Washington, DC, and I'm professor of pediatrics at the George Washington University School of Medicine.

DR. MASUR: Henry Masur, chief of critical care medicine at the Clinical Center-NIH.

DR. BENNETT: Jeff Bennett, chief of the clinical oncology section and an infectious disease clinician at NIH.

DR. D'AGOSTINO: Ralph D'Agostino, professor of mathematics, biostatistics, and epidemiology at BU.

DR. CAPPELLETTY: Diane Cappelletty, infectious diseases pharmacist at the University Toledo Medical Center, and associate professor in the University of Toledo College of Pharmacy.
DR. WEINSTEIN: Mel Weinstein, professor of medicine and pathology and chief of infectious disease at Robert Wood Johnson Medical School in New Brunswick, New Jersey.

MS. YOUNG: Kathy Young, health care policy specialist, former director of strategic planning at BlueCross, BlueShield and at the Mass Hospital Association, and executive director of the Alliance for Prudent Use of Antibiotics.

DR. CHATTERJEE: Archie Chatterjee, professor of pediatrics and chief of pediatric infectious diseases at Creighton University School of Medicine.

DR. MOORE: My name is Tom Moore. I'm the chairman of today's meeting. I'm also chief of infectious disease at Oxford Medical Center in New Orleans, Louisiana.

DR. DOAN: I'm Minh Doan. I'm designated federal officer of the Anti-Infective Drugs Advisory Committee.

DR. FOLLMANN: I'm Dean Follmann, head of biostatistics at the National Institute of Allergy
and Infectious Diseases.

DR. NEELY: I'm Michael Neely. I'm a specialist in pediatric infectious diseases and pharmacometrics at the University of Southern California, Los Angeles.

DR. GOETZ: Matt Goetz, chief of infectious diseases, VA Hospital, Los Angeles, professor of clinical medicine, UCLA.

DR. FRATZKE: Jim Fratzke. I'm a retired dentist from Portland, Oregon, and I'm serving as the patient representative.

DR. FLEMING: Thomas Fleming, Department of Biostatistics, University of Washington.

DR. RELLER: Barth Reller. My background is medicine and infectious diseases and medical microbiology. I'm in the Division of Infectious Diseases and International Health and professor of medicine and pathology at Duke University.

DR. KOMO: Good morning. Scott Komo, statistical reviewer in the Office of Biostatistics, Division of Biometrics, for the FDA.

DR. TOERNER: Joe Toerner. I'm the
associate director for medical affairs in the Office of Antimicrobial Products at CDER-FDA.

DR. LAESSIG: Katie Laessig, deputy director, Division of Anti-Infective Products, FDA.

DR. FARLEY: John Farley, acting director, Division of Anti-Infective Products, FDA.

DR. COX: Ed Cox, director of the Office of Antimicrobial Products, CDER-FDA.

DR. MOORE: Thank you.

Dr. Roberts, who was here yesterday, was supposed to join us today, but he is unable to join us. I note that for the record.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.
In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, the FDA will refrain from discussing the details of this meeting with the media until its conclusion.

For the convenience of the media representatives, I'd like to identify the FDA press contact, Lisa Kubaska. There she is on the end. Thank you, Lisa.

Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Now, I'll pass it to Minh Doan, who will read the conflict of interest statement.

**Conflict of Interest Statement**

**DR. DOAN:** The Food and Drug Administration is convening today's meeting of the Anti-Infective
Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 USC Section 208 and Section 712 of the Federal Food, Drug, and Cosmetic Act, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary members of this committee are in compliance with federal ethics and conflict of interest laws.

Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services
outweighs his or her potential financial conflict of interest.

Under Section 712 of the Food, Drug, and Cosmetic Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussion of today's meeting, members and temporary members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 USC Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves discussion of clinical trial design issues in the development of antibacterial drugs for the treatment of hospital-
acquired bacterial pneumonia, including ventilator-associated bacterial pneumonia and the draft document entitled, Guidance for Industry: Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment, published November 2010.

This is a particular matters meeting during which general issues will be discussed. The committee will not be voting. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary members, no conflict of interest waivers have been issued. A copy of this statement will be available for review at the registration table during the meeting and will be included as part of the official transcript. To ensure transparency, we encourage all standing committee members and temporary members to disclose any public statements that they have made concerning the topic at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. John Rex is participating in this meeting as a
non-voting industry representative, acting on behalf
of regulated industry. Dr. Rex's role at this
meeting is to represent industry in general and not
any particular company. Dr. Rex is employed by
AstraZeneca.

With regard to FDA's guest speakers, the
agency has determined that the information to be
provided by these speakers is essential. The
following relevant interests are being made public to
allow the audience to evaluate objectively any
presentation and/or comments made by the speakers.

Dr. Donald Craven has received funding from
Pfizer for clinical research. In addition, he has
served as a scientific advisor, consultant, or
speaker for Cubist, Merck, Pfizer, and Sanofi
Pasteur.

Dr. Robert Fromtling is employed by and
holds stock in Merck & Company.

Dr. Thomas File has received funding from
Forest Laboratories, Pfizer, and Cempra
Pharmaceuticals for clinical research of drugs for
the treatment of community-acquired pneumonia. In
addition, he has served as a scientific advisor and consultant for Bayer, Daiichi/Sankyo, Merck, Pfizer, GlaxoSmithKline, Nabriva Therapeutics, and Tetraphase Pharmaceuticals.

We would like to remind members and temporary members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with the affected firms.

Thank you.

DR. MOORE: Thank you, Minh.

We'll now move on to the FDA presentations.

Dr. Cox?

FDA Presentation - Edward Cox

DR. COX: Thank you, Dr. Moore, and welcome, everybody, to our second day of this Anti-Infective Drugs Advisory Committee. We appreciate everyone
coming. We appreciate the committee getting a good
night's sleep and getting ready to dig in on a second
day.

So today we'll move on, and we'll talk about
hospital-acquired bacterial pneumonia and ventilator-
associated bacterial pneumonia. And as you'll see as
we work through the issues and topics through the
course of today's discussion, many of the issues are
conceptually very similar to what we talked about
yesterday with regard to community-acquired bacterial
pneumonia.

The disease is a little bit different.
There are some slightly different specifics. But
we've brought this issue, too, because like
yesterday's issues, there are some inherent
challenges to designing clinical trials to study a
new drug for hospital-acquired pneumonia and
ventilator-associated pneumonia. Many of these stem
from the biology of the disease; again, an acute
infection where therapy needs to be started promptly.
And many of these patients may have a number of
medical problems, comorbidities going on
simultaneously; questions about the effects of prior therapy, another issue here for discussion; and that of diagnostic uncertainty given that patients with hospital-associated pneumonia and ventilator-associated pneumonia may be -- there may be multiple things going on. It may be somewhat challenging to make the diagnosis, and we'll have some discussion about that, too.

Again, too, I think as we've tried to work through this issue, as we've put out a draft guidance document, received comments, and had an opportunity for a workshop, I really do think we have learned more about the disease and the disease condition, and that's been helpful in moving things along. We'll look to build on those discussions further here today.

Again, for hospital-acquired pneumonia and ventilator-associated pneumonia, clearly, an area where additional therapies are needed to treat patients today who would benefit from having additional therapeutic options, and we certainly can expect that that will happen in the future. And,
too, if we think about the development time and
development cycle for a new antibacterial drug, it
does take a period of time, somewhere between 5 and
10 years; so another thought to be mindful of as we
consider the need for new options.

Factors driving new options: antimicrobial
resistance and patient tolerance to allergies, drug
interactions, and, also, the adverse event profiles
with better tolerated options are always a real plus.
And beyond that, too, would be options that do add on
the efficacy side, too, options that may be able to
achieve better outcomes. As always, prudent use is
key for any antibacterial drugs, those that we have,
those that may be developed in the future.

Similar to the discussion yesterday, for
trial designs for HABP/VABP, what we're trying to get
to is scientifically sound, ethical and feasible
trial designs. Similar to CAP, also, in this
setting, non-inferiority trials will be the type of
trials that one would expect to typically see, and
that puts us in the situation of needing to have an
evidence base for the non-inferiority margin that we
use for these trials.

As we've looked around at a variety of different disease conditions to try and understand treatment effect, we often find that there are limitations to the available information. We certainly do our best to use that information to try and understand what the treatment effects are and use that as the basis for defining non-inferiority margins. And you'll hear some discussion about the work that has been done, and some of it has been previously discussed, to try and understand treatment effect for antibacterial drugs for hospital-acquired pneumonia and ventilator-associated pneumonia.

Similar to the discussions yesterday, one of the things that we're aware of are the issues with regard to feasibility and practicality for clinical trial designs for studying drugs for hospital-acquired pneumonia and ventilator-associated pneumonia. The comments to the docket have brought up some of the particular challenges with trying to conduct these studies.

I look at this as almost sort of being
inherent in the process and that there are some tradeoffs with regard to the precision of the efficacy and safety estimates, the size of the trial, in essence, for a drug and some tradeoffs of practicality and feasibility. And really what we want to get to are feasible, practical trial designs, but we still need to maintain scientifically sound trials, trials that are ethical, and designs that will allow us to assess the safety and efficacy of new drugs for hospital-acquired pneumonia and ventilator-associated pneumonia.

Similar to what we have done with the background materials yesterday and through the discussions yesterday, you'll notice today that we've also tried to provide three options; again, not meant to represent all the possible options, but meant to represent a few different options that we put out there that we hoped would be food for thought as the committee discusses these issues.

So we tried to frame options 1 through 3, and we seek your advice on these options, and you'll see the questions are built around those options.
And the options and the questions bring up issues with regard to particular non-inferiority margins, prior antibacterial therapy, how that should be addressed, what the development program might look like for the phase 3 program, number of trials, whether it's a HAPB trial, whether it's a HAPB and a VAP trial, whether it's just a VAP trial, and what the indication might be, depending upon the approach that's taken with regard to the particular indication study, whether it's just VAP, whether it's just HAPB.

Then also the timing of the endpoint. The background materials discuss a 28-day mortality endpoint. The question open to the committee, is that the right point in time that we should be looking at that particular endpoint.

So I'll just run through the questions so that folks have a feel for where we're headed over the course of the day.

Question 1. Please discuss the merits and limitations of the single trial plus supportive information proposal for hospital-acquired bacterial pneumonia, ventilator-associated bacterial pneumonia.
Please discuss the types of supportive evidence that would be considered acceptable if only a single HABP/VABP trial is conducted.

You'll see in the background materials, in Section F outlines option 1 and option 2. Option 1 is essentially a VAP-based option. Option 2 is a HAPB-based option. And then it also provides information about potential types of information that might be supportive. And what we've put out there for discussion is a study in another indication, such as complicated intra-abdominal infection, I think we've got community-acquired pneumonia, and then also skin infections in the setting of a Gram-positive agent. So that's question 1.

Question 2 moves on to the non-inferiority margin and then brings into the discussion the issue of what the mortality rate is that's observed in the trial and the control arm of the study. So please discuss if the non-inferiority margin of 10 percent will be acceptable if the active control mortality rate is less than 20 percent. Please discuss if the odds ratio or risk difference metric is preferred.
when the control mortality rate is less than 20 percent. And through the presentations today, you'll hear some discussion of the mathematical properties of these different metrics for assessing the statistics of the trials.

Question 3, this gets to the issue of timing for endpoint assessment and is directed toward the all-cause mortality endpoint. Please discuss the preferred timing for the all-cause mortality endpoint. Would an assessment at an earlier time point be preferred for the 28-day assessment? And that's the 28-day assessment of mortality.

Question 4 gets to the issue of prior antibacterial drug therapy. Please discuss the following scenarios regarding use of prior antibacterial drugs. So if empiric antibacterial treatment for HABP/VABP has begun prior to enrollment in the trial, what duration of therapy would be acceptable and unlikely to confound the interpretation of the treatment effect of the study drug? Please describe your rationale. Please discuss what other information might be useful to
address this question.

So if there are thoughts on other information that might help to further address this, that would be appreciated. And here what we're talking about is empiric antibacterial drug therapy that would be effective in the treatment of the particular pneumonia that the patient is having, the current episode.

The B part, should a patient who develops HABP/VABP while receiving antibacterial drugs for other infections be enrolled in the HABP/VABP trial? If so, please discuss some scenarios where this will be acceptable.

So this gets to the issue of if a patient has another infection, they're in the ICU, and while being on the other antibacterial drug therapy, they develop a pneumonia. So issues such as the duration of the prior therapy, the particular organism that's isolated as the cause of pneumonia, the relation to the prior therapy they may have received for the other infection; those sorts of topics seem like they would be issues for discussion as they relate to the
B section of question number 4.

So I'll stop there and turn it back to Dr. Moore. Thank you.

DR. MOORE: Thank you, Dr. Cox. Let's move on to Dr. Toerner.

**FDA Presentation - Joe Toerner**

DR. TOERNER: Dr. Moore, thank you very much and good morning. And I'd also like to thank the members of the committee for being here and spending the time and effort to discuss hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia. And I'll be going through a regulatory background that is summarized as follows. I'll provide a summary of the workshop discussion that took place in 2009. I'll then go through some highlights of the draft guidance document, and then provide a summary of the comments that we received in the docket in response to the draft guidance document.

In the early spring of 2009, a workshop that was cosponsored by the Infectious Disease Society of America, the American Thoracic Society, the Society
for Critical Care Medicine, and the American College of Chest Physicians, and the FDA, took place with the goal to discuss the scientific data addressing key issues in the design of clinical trials for treatment of patients with HAP and VAP. And the proceedings of the workshop can be found in a supplement, August 2010, of Clinical Infectious Diseases.

So I'll be providing just a very high level overview of the workshop and the discussions at the workshop. So this just lists some of the presentations that were given. There was a presentation about trial designs, with a particular focus on the non-inferiority trial design. There was a review of published studies and an assessment of treatment effects of antibacterial drugs in the management of patients with HAP and VAP.

There was a review of recently conducted registrational trials; current therapies for treatment of patients with HAP and VAP, including antibacterial treatments, as well as non-antibacterial therapies that was presented. Diagnostic evaluations and microbiologic etiologies
were two areas of presentations. And there were perspectives at the workshop from FDA, from industry, from academia and the professional societies that participated in the workshop.

There were a total of 16 discussion questions. In terms of the discussion questions, I'm going to provide just the highlights that are pertinent to the discussion topics that we'd like you to address today.

So, in general, it was felt that evaluating new drugs for an indication for treatment of HAP and VAP is very challenging. There have always been efforts to minimize hospital-acquired infections, but those efforts have been intensified over the past several years.

The Center for Medicaid and Medicare Services has issued proposed rules that describe a lack of reimbursement for patients with ventilator-associated pneumonia. It's my understanding those were not included in the final rule, yet it still is on the radar screen for these types of pay-for-performance criteria.
The Joint Commission has as part of their hospital accreditation a requirement, if you will, that hospitals document hospital-acquired infections and document and evaluate their efforts to reduce hospital-acquired infections. So these efforts make evaluation of patients with HAP and VAP challenging because we may find the incidence is decreasing.

It was recognized that trials obviously would be multi-center trials. The bacterial etiologies among the different centers differ. The management strategies of patients in the intensive care unit differ among the different centers, and it just makes implementing a single protocol very challenging in a multi-center setting.

The important topic that was discussed at the workshop was endpoints, and we put forth in our presentations an all-cause mortality endpoint as an efficacy endpoint, and we could find a treatment effect; based upon the review of historical studies, a very large treatment effect on an all-cause mortality endpoint in patients who were inadequately treated for HAP and VAP versus patients who were
appropriately treated for HAP and VAP.

Most of the discussants at the workshop were in favor of this type of endpoint. But if you were present at the workshop and even if you read through the transcripts, the endpoint did not receive overwhelming enthusiastic support. And a lot of this lack of enthusiasm dealt with concerns that when you're evaluating mortality in this particular patient population, the mortality may not be due to respiratory events, but in a patient population with significant comorbidities, mortality may be due to other non-respiratory events. But when discussing the all-cause mortality endpoint, the timing that was most often discussed as an appropriate timing is somewhere between 14 days and 28 days.

The other clinical non-mortality endpoints were discussed at the workshop, and just some examples provided here are days spent in the intensive care unit, days spent on mechanical ventilation, the ratio of the arterial oxygenation to the fraction of inspired oxygen. Those were felt to be important clinical events to monitor.
But the review of the historical information from studies previously conducted, there was a lack of a consistent evaluation in those studies about clinical endpoints. And so we could not identify a treatment effect based on non-mortality endpoints.

It was recognized that trials should be active controlled, randomized, blinded, and could be superiority or non-inferiority, but it was the mortality endpoint that was felt to have an endpoint for which there is evidence of a treatment effect that would support the non-inferiority trial design.

It was discussed whether or not patients with HAP and patients with VAP could be included in the same trial or whether they should be evaluated in separate trials. There was not a strong consensus reached. There were strengths and weaknesses of either approach.

The workshop also discussed the definition of HAP and VAP. The discussion included that trials should be enriched for patients who have bacterial disease or hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia. And as an
example, the CPIS score, the clinical pulmonary infection score, of greater than 6 is more likely to be associated with diagnosis of ventilator-associated pneumonia. So that was one way to enrich for a population to ensure that you have VAP.

It was generally felt that the microbiologically confirmed intent-to-treat population should be the principal analysis population, and it was noted that it would be easier to obtain a microbiologic specimen for confirmation in patients on mechanical ventilation.

There was a point and counterpoint approach to the role that quantitative cultures might play in this diagnosis, and there was no strong consensus that was reached on the role that quantitative cultures might play in the design of clinical trials for patients with VAP.

As well at the workshop, it was recommended to enroll patients with sufficient severity of disease at baseline and to stratify for that, and that was really pertaining to the all-cause mortality endpoint to ensure a patient population with a
sufficient severity of disease.

There were different scoring systems that were discussed, for example, the APACHE-II scoring system, but there were strengths and weaknesses that were discussed among the many different scoring systems that were presented at the workshop.

The issue of concomitant therapy poses unique concerns, and it was recognized that empirical broad spectrum antibacterial coverage is important for patients newly diagnosed with HAP and VAP, and that aminoglycoside therapy is often administered concomitantly, in particular, in patients with pseudomonas aeruginosa infections. Although de-escalation of antimicrobial therapy is recommended on the basis of the results of in vitro susceptibility testing, it was noted that de-escalation is rarely done in the clinical setting.

As well, at the workshop, the issue of establishing safety and efficacy in the pediatric population should be done and discussed with FDA as early in product development as is possible. And the consortia or cooperative groups could enhance
protocol development and implementation in this area.

So now I'm going to turn your attention to the draft guidance document. We prepared the draft guidance document and incorporated the topics that were discussed at the workshop into the guidance. We included a summary of the work that was done to justify the non-inferiority margin, and the draft guidance was issued in November of 2010. And as with all draft guidance documents, we outlined a 90-day comment period before we initiate the work done to finalize the guidance. But it's noted you can comment on our guidance documents at any time.

So now I'm just going to highlight some of the important features of the draft guidance document. Again, it'll be pertinent for the discussion today. So we did outline an enrollment criteria that patients should be sufficiently ill such that a mortality rate of approximately 20 percent would be expected in the control group.

We defined hospital-acquired bacterial pneumonia as patients being hospitalized for at least 48 hours, or if they had been discharged from the
hospital and developed pneumonia, that that discharge
occur within seven days. For ventilator-associated
bacterial pneumonia, we defined that as patients
having had mechanical ventilation for at least 48
hours, and, as mentioned previously, we outlined a
CPIS score of greater than 6, which would enrich for
a population with having ventilator-associated
bacterial pneumonia in contrast to other acute
pulmonary processes that occur in this patient
population.

New radiographic findings and clinical
criteria that are associated with HABP and VABP were
outlined as enrollment criteria in the draft
guidance, and the criteria of sputum examinations
that would allow an appropriate microbiologic
identification were outlined in the draft guidance.

For the efficacy endpoint, we described a
28-day all-cause mortality endpoint as the primary
efficacy endpoint. This would be used in active
control trials designed for non-inferiority. And in
the appendix to the guidance, we provided
justification for the non-inferiority margin.
In the guidance, we recommended that trials enroll only patients with VABP or that trials enroll only patients with HABP. But we noted that a clinical development program that described safety and efficacy in VABP would support an indication for treatment of both HABP and VABP and that a clinical development program that had evaluated patients and established safety and efficacy in patients with HABP would support an indication for treatment of HABP.

We also outlined the microbiologically confirmed intent-to-treat population as the primary analysis population. And, again, based on the discussion at the workshop, we went back to the historical literature to look at the non-mortality clinical endpoints. Again, we could not find support for a treatment effect based on any other endpoint other than all-cause mortality.

Nevertheless, the discussion had highlighted the importance of these clinical endpoints in the management of patients with HAP and VAP. So we included them as secondary endpoints; for example, the clinical cure or the complete resolution of signs.
or symptoms, the ratio of arterial oxygenation to the fraction of inspired oxygen, improvement over time, and then a clinical progression or administration of rescue antibacterial drug therapy could be defined as clinical failures on secondary endpoints.

Other considerations in the guidance. Based upon the data that you heard yesterday on the administration of prior antibacterial drug therapy, we outlined the exclusion of patients who have received prior antibacterial drug therapy that has activity against pathogens that cause HAP and VAP.

We acknowledge that empirical use of antibacterial drug therapy is appropriate for patients newly diagnosed with HAP and VAP to provide broad spectrum antibacterial coverage. But we outlined a recommendation to avoid concomitant antibacterial drugs that would have overlapping activity with the investigational drug.

We also provided a brief discussion of clinical trial designs in patients with unmet need; that is, patients who have a bacterial pathogen that, on in vitro susceptibility testing, has shown
resistance to multiple antibacterial drugs. And we outlined in the description of the clinical trials findings of superiority of the investigational drug. So now I'll turn your attention to the comments that we received in response to the draft guidance document, and there were 14 responses submitted to the docket. Most of the responses were from the pharmaceutical industry. Some were from individuals. And before I go on, I just wanted to point out that we consider all comments when we work toward preparing the final guidance document, and we thank you very much for submitting the comments to us. It's very helpful to us when we work toward finalizing a draft guidance document.

We included all of the comments to the docket in your background materials. And we found it helpful to characterize the comments into nine particular areas of criticism. There were common themes among the 14 responses that we received. So these nine general areas included that we put forth a guidance document that's not practical for sponsors to consider drug development for these indications.
There was criticism of the all-cause mortality endpoint. There were concerns about how we approached the statistical considerations for the primary endpoint. There were comments about the comparator antibacterial drugs that we had described in the draft guidance. There were issues with the use of prior antibacterial drugs. The trial population considerations garnered some comments to the docket; clinical microbiology considerations. Entry criteria concerns were also areas where there were comments to the docket. And, finally, there were comments that addressed our brief description of clinical trials in patients with unmet need.

Now, for the rest of the discussion today, I'm going to focus on five particular areas. That's not to say the other four areas are unimportant. They are very important. But we feel in the other four areas that the comments we received were straightforward, and we can easily address them as we move toward finalizing a guidance.

Just as one example, the issue of including the results of a sputum examination from a mini
bronchoalveolar lavage, we did not include that in
the draft guidance, and we can certainly incorporate
that into the final guidance. But for today's
discussion, we thought it important to focus on these
five particular areas.

So I grouped the first two areas together
because a lot of the concerns, in general, that we
issued guidance that was not practical pointed to the
use of the all-cause mortality endpoint. And these
bullet points are just very few examples of the
criticism of the all-cause mortality endpoint.

As a common theme, many felt that there were
advances in the management of patients in the
intensive care unit, even within the past couple of
years, such that mortality rates are less than
20 percent. The comments thought that our
requirement for the microbiologically confirmed
intent-to-treat population may make trials too large.
There was uncertainty about the timing of the day 28
all-cause mortality endpoint. And, again, this is
just a few representative examples of the criticism
of the all-cause mortality endpoint.
There was a criticism to our approach to the statistical considerations. Some felt that our discounting was extensive to arrive at a non-inferiority margin. Some felt that a 12.5 percent non-inferiority margin was supportable based on the information we provided in the appendix section, and there were questions about our choice of an odds ratio metric of 1.67.

As well, there were concerns about large sample sizes, in particular, with the strong suggestion in the draft guidance that two adequate and well controlled trials would be recommended for this indication.

There were comments about the comparator antibacterial drugs; that treatment guidelines for patient management, even if those guidelines had been issued fairly recently, they might not be relevant today as changes with in vitro susceptibility tests among the bacterial pathogens change and can change quickly over time.

There were concerns that our recommendation for using FDA-approved antibacterial drugs was too
restrictive, that there may be some antibacterial
drugs that are approved for use in countries outside
the United States, and so we should allow some
international flexibility. And the dosages that are
used in the management of patients with hospital-
acquired and ventilator-associated pneumonia may be
different than what's recommended in product
labeling.

Then the issue of prior antibacterial drugs,
and you've heard the rationale yesterday for why we
felt it important to exclude patients who received
prior antibacterial drugs pertaining to community-
acquired bacterial pneumonia. And so some comments
pointed out that excluding prior use was unjustified
in this particular setting and is impractical, and
that peri-operative antibacterial drugs are commonly
used in patients, in particular, trauma patients and
patients in a surgical intensive care unit. And so
these would limit an ability to enroll patients in a
trial of HAP and VAP.

So now I just wanted to summarize the
comments that we received to the docket and how they
pertain to the discussions today.

So there was a lot of criticism about the all-cause mortality endpoint, and the docket comments had suggested that we use a clinical endpoint other than all-cause mortality. And just as we did for community-acquired bacterial pneumonia, where we went back and looked through the historical literature and we were able to -- on closer examination able to find a treatment effect earlier in the course of therapy for community-acquired bacterial pneumonia, we went back again and did that same approach for hospital-acquired and ventilator-associated pneumonia; yet, again, we were unable to find support for a treatment effect on an endpoint other than all-cause mortality endpoint.

But we recognize that there are issues with the use of the all-cause mortality endpoint. And so in subsequent talks today and for your discussion, we'll consider these issues when the all-cause mortality rate in the control group is less than 20 percent and also discuss the timing of the all-cause mortality endpoint.
As well, the concerns about the approach that we used in our statistical considerations, we'll have some discussion and further presentations today on the microbiologic intent to treat analysis populations. I think you'll find that the situation is very different for HAP and VAP in comparison to CAP, where a greater proportion, you can identify a microbiologic etiology.

Also, we'll provide further discussion for you on the approach to the non-inferiority margin and the differences between the risk, difference in the odds ratio, and try to further explore that with you later on this morning. And then as you saw in the background materials and with our discussion question, what's the role of a single trial with other supportive data for this indication, again, keeping in mind what Dr. Cox just went through, the issues of a clinical development program being scientifically sound, ethical, and feasible. And then, finally, to discuss the issues surrounding prior antibacterial drug and the role of the comparator drug in trials of patients with HAP and
VAP.

So that will complete my talk today. I wanted to thank my FDA colleagues that are listed on this slide who helped in the preparation of the draft guidance document. And I'll turn it back over to Dr. Moore.

DR. MOORE: Thank you, Dr. Toerner.

With that, let's move on to Dr. Craven to start off the guest speaker presentations.

Is Dr. Craven present?

[No response.]

DR. MOORE: All right. We ended a little early, which is fine. We'll take advantage of that.

Is Dr. Floyd ready to roll? We'll move you up and come back to Dr. Craven in a bit.

**Guest Speaker Presentation - James Floyd**

DR. FLOYD: I'm James Floyd. I'm a general internist and pharmacoepidemiologist, and today I'm representing Public Citizen. It's a consumer advocacy organization with an interest in the evaluation of safety and efficacy of drugs and medical devices.
Here's an outline of my talk. And today the discussion is going to be about the draft guidance on HAP/VAP, and there are a few major issues that I want to comment on. One is mortality as the endpoint. Another is micro intent to treat as the primary analysis; and next, the use of prior and concomitant antibiotic therapy.

I'm not going to go over the things I went over yesterday. Obviously, there are a number of trial designs. As I explained before, a non-inferiority trial is not the ideal design, but for practical reasons, this is probably what will be done. An aim is to show that a new investigational drug is not worse than an existing effective therapy by some unacceptable margin.

Again, I'm not going to go through the elements of a well done non-inferiority trial. But I want to say that because it's so hard to do one well, the issue isn't generalizability, whether the trial reflects what we do in practice. The major concern is whether you can show in a trial that a drug doesn't work, and you have to do that before you can
worry about concerns about extrapolating to other populations.

So as discussed yesterday, there was a lot of talk about what's a valid clinical endpoint to determine efficacy. This doesn't mean that other signs or biomarkers aren't very useful clinically and that we aren't going to continue to use them, but to determine the efficacy of a drug, you need something that is well defined and reflects, to some degree, how a patient feels, functions, or survives.

In addition, in a non-inferiority trial, you actually have to have some evidence that on this endpoint, your active comparator has some therapeutic effect. I would argue that in HAP/VAP, as FDA has shown and as there's been previous discussions, the only endpoint for which we have this that meet all of those criteria is all-cause mortality. And I don't know if we're going to revert to some discussions about all-cause versus attributable mortality, but I think it's worth touching on very briefly.

So when I say mortality, I mean all-cause mortality. And the main rational for using an
attributable mortality is because of power. It's much easier statistically to show a difference between a 10 and 20 percent difference in an event rate versus a 20 or 30 percent or 30 and 40. So it will decrease the sample size. But the downside is it's very difficult to tell what causes a death. There is potential for ascertainment bias, and it's likely that you'll have very few events. So for all those reasons, that's not an ideal endpoint in attributable mortality.

There's also been some comments in the past about confounding, and I want to clarify this. Patients dying of things not directly related to a HAP or a VAP is not confounding. In fact, that's the point of doing a randomized trial so that predictive factors of death, such as heart failure, other things like that, are balanced. So it's not an issue of confounding. It's an issue of statistical power.

Also, as we discussed yesterday, a test of cure endpoint, while it might be of use to look at, it's not valid in a primary efficacy determination. It includes a lot of signs and biomarkers that are of
interest clinically and that we use to manage
patients, but they're not things that are well
measured and aren't things that we have evidence of a
treatment effect for the active comparator.

As was discussed yesterday, it's ideal to
look at those things as a secondary endpoint, if you
want to know that signs are resolving, because this
actually makes the evaluation more rigorous. You
show that on your primary endpoint, you've met non-
inferiority, and then it's fine to look at these
other things to reassure yourself that you're not
having complications like empyema or late effects.
But it's not okay to combine these things in a
composite endpoint, because that makes the evaluation
less rigorous.

Yesterday I went over the rationale for our
margin. Of course, there are statistical
considerations. You need evidence of effectiveness
for the active control, but then you have to make a
clinical judgment about how much harm is tolerable.
This is not a statistical concern. This is a
clinical judgment.
I gave a rationale for why it's difficult to justify more than a 10 percent worsening in an endpoint. And, certainly, if you're talking about mortality, I think it's very difficult to justify a new therapeutic that may be 15 or 12 and a half percent less effective than an existing effective therapy. And certainly when you contrast that to things that we consider to be highly effective therapies, like aspirin or PCI after ST elevation/MI, I think it's even more difficult to justify a very large margin.

So a little more about the margin. What margin is appropriate and does this depend on the mortality rate? If you have a population with a 20 percent mortality in the control group -- and we have pretty good evidence that existing effective therapies can do this -- and you set your margin at 10 percent, you preserve half of the treatment effect.

If your mortality is less than 20 percent and you stick with a 10 percent margin, you're preserving less than half of that treatment effect.
And if your control group mortality is down to 10 percent, you actually preserve none of the treatment effect. So this risk difference metric for a margin is problematic, and I think Dr. Komo is going to discuss this further in his talk.

Now, one alternative is to use an odds ratio metric. And I agree with FDA, this is a good idea. And you can do this for CAP, as well. This is not specific to HAP and VAP. I'm reproducing a figure from the FDA materials here, I hope that's okay. And on the X-axis here, you have the mortality rate in the control group. And at 20 percent, you can see a risk difference margin of 10 percent, an odds ratio margin of 1.71 is equivalent to a 50 percent increase in risk, effectively preserving half of the treatment effect.

Now, if the mortality decreases as you go left on the graph, you can see that risk difference, which is red, increases. And if you get to 15 percent, that 10 percent margin is allowing a 68-67 percent increase in risk of death. If you push that all the way to 10 percent, it goes to 2.0, which
preserves none of the treatment effect.

The odds ratio is in blue, and it's not perfect, but it's, in fact, far more robust. So if you have a mortality rate that's low in the control group, lower than the 20 percent that you would like, it's ideal to use an odds ratio metric. In fact, you could use an odds ratio metric to start out with, whether your mortality rate is 20 percent, 25 percent or 15 percent.

So as far as study population, as with community-acquired pneumonia, the ideal population are those with microbiologic evidence, actually any evidence of the bacterial pathogen that's typical in HAP and VAP. It does not need to be culture. Certainly, the incentive is to create diagnostics that can identify other pathogens. And this is a methodologic concern primarily. I think if you're doing a non-inferiority trial, you need to study people for which you have evidence of a treatment effect. The failure to do so will bias you in favor of a similar treatment effect, and you can declare non-inferiority when you have an ineffective therapy.
Now, related to this is -- to what population to analyze is how many trials to do. I agree with FDA that it's ideal to do separate trials in HAP and VAP. But if a single trial were done looking at both diseases, you still need independent confirmation somewhere. And this is not just a regulatory concern. This is true in science throughout. If you have a finding, you need to validate it, substantiate it in an independent setting. So if you do another trial looking at both diseases, you need to have another setting, another trial with a similar endpoint, with a similar outcome that can substantiate that initial finding.

I want to give one example that kind of shows the pitfall of not confirming a finding in one trial. So Xigris, activated protein C, was approved for the treatment of severe sepsis based on the subgroup of one trial. And this was promoted heavily. Unfortunately, it was not used widely. And when a second trial was done, it actually showed no treatment effect, suggesting strongly that this initial trial result -- the subgroup analysis of that
initial trial was spurious.

Now, this is probably going to be the most contentious issue today, whether to tolerate prior antibiotics or concomitant antibiotics and what implication does this have to declaring a drug non-inferior.

So I want to contrast community-acquired pneumonia with hospital acquired pneumonia. I'm a hospitalist, so community-acquired pneumonia is a pretty bread-and-butter disease for me. It's pretty uncommon to take care of people who have gotten a course of antibiotics before they come in. This is mostly a logistical concern with people getting antibiotics in the emergency department and not enrolling them quickly enough. In contrast, in hospital and ventilator-associated pneumonia, it's actually common that people have other infections and get antibiotics. I realize that. Nonetheless, if you have people who get therapy right before you randomize them, you are going to bias your trial in favor of non-inferiority. That's a serious concern.

Now, FDA has proposed a 30-day window during
which you can't receive prior antibiotics. It may be reasonable to shorten this. And if this has dramatic effects on enrollment, I would encourage the FDA to look into this. And depending on the half-lives of the drugs given before they're randomized, a 14 or a 7-day window could be tolerable, even shorter, but I think that's worth exploring, and I think it probably will have an effect on enrollment.

Now, I think the more problematic issue is the use of concomitant therapy with overlapping spectrum against HAP/VAP pathogens. Now, even though I don't think it's well supported by evidence, it's very common practice for people to receive multiple antibiotics. Just like prior antibiotics, this is going to bias you in favor of a non-inferiority finding. It's going to make two treatments look alike even when one is not effective or less effective than the other.

I'm not sure what the correct answer is for this, but I think the FDA outlines a scenario where this is okay. If you have a narrow spectrum drug that doesn't overlap with your concomitant therapy,
you could actually evaluate this in a non-inferiority trial. The caveat would be that your drug is approved for concomitant use with this other drug. It's not okay to use as monotherapy.

Again, the issue is not generalizability, whether we give these drugs in combination in practice; it's about internal validity of the trial you use to determine efficacy. And if you give therapies together that are active against the disease you're studying, you're going to make it impossible to term it non-inferiority, even if you have similar outcomes, even if you study a very good endpoint like mortality.

I'm going to give an example that I think will come up for discussion later today. So doripenem was not approved for HAP/VAP, but it was studied, and I've listed some of the results from the phase 3 trials, from the briefing document when this came up a few years ago.

I don't remember if prior antibiotic use was a big problem, but one thing that did occur was a very high rate of use of amikacin for possible
pseudomonas infection. My laser pointer is not
working, but if you look in the second row here,
78 percent of the doripenem group got amikacin,
85 percent of the Zosyn group didn't. And this is a
drug that has overlapping spectrum of activities,
active against HAP/VAP pathogens.

Now, down here you have the results for test
of cure. The results look pretty similar. In fact,
if anything, they looked a little better for
doripenem, and this is just one of the two trials.
But when you look at mortality in the safety
analysis, it was higher. In fact, it was twofold
higher in the doripenem group. And I think this is
an illustrative example of how, if you give
concomitant therapy, you may obscure your ability to
see a difference in treatment effect.

Now, some people may say, hey, well, we
found mortality difference. It could be it's an off-
target effect of the drug; it has some toxicity.
But, alternatively, if it was because a drug was
highly ineffective, the mortality difference could
have been even larger. The fact that you gave
amikacin to almost everyone in the trial really impaired your ability to detect a difference.

So to conclude, I think, in general, the draft guidance is a good document, and I think the FDA has gone a long way to making sure that these trials are done in a way that you can detect a treatment effect, that you can show that an ineffective drug doesn't work, and you can say with confidence that if you meet your margin, that your new therapy is effective.

To reiterate, I think the only credible endpoint for efficacy that we have evidence of a treatment effect for an active control is all-cause mortality. As with all indications, the non-inferiority margin should be justified. And I think that you should strongly consider the odds ratio metric. I think that is robust, two different mortality rates in your trial, and it's a good solution.

As with CAP, the study population should be valid. And I don't have the answers, but the use of concomitant therapy is very problematic in these
trials. And I would agree with FDA that you should not allow the use of antibiotics prior to randomization.

Thank you.

DR. MOORE: Thank you, Dr. Floyd.

I believe Dr. Craven is here.

Dr. Craven, we'll go ahead and take your presentation now. Thank you.

I should point out that Dr. Craven -- just as with yesterday, I failed to do this. Dr. Craven is representing the Infectious Disease Society of America. Thank you.

**Guest Speaker Presentation - Donald Craven**

DR. CRAVEN: Thank you very much. Good morning, everyone. For the next 20 minutes, my chore is to talk about clinical trials, particularly as they relate to ventilator-associated pneumonia, also known as VAP, and hospital-acquired pneumonia, which is called HAP. I'm going to talk about definitions, diagnostics, and outcomes.

Here are my disclosures. I'm on the speaker's bureau for several different pharmaceutical...
companies, shown here. We have research support for
previous trials from Bard and Pfizer, and I have some
honorary and consulting associations with PhRMA.

I'm going to be using a lot of terms. Many
of you probably are not familiar with these terms,
but I'm going to use the term VAP and HAP, which I
just defined for you, hospital-acquired pneumonia,
which I'm sure you've heard several times this
morning.

But I'm going to be talking a lot about
microbiology, because if we're going to be looking at
the effect of an antibiotic in treating pneumonia, we
really need to know what organisms are causing
pneumonia. And I'm going to talk about what I call
quantitative tracheal aspirates. That's in
ventilated patients, putting a suction catheter down
and taking sputum out of the lower airway. This is
also what's known as semi-quantitative. Many
hospitals in the United States don't use
quantitative, but they use semi-quantitative. So I'm
going to show you how that can be used appropriately
and effectively in clinical trials. And then some
hospitals, including our own, use bronchoalveolar lavage, where you put a catheter down, lavage out the distal airways to try to get samples from the lung parenchyma. I'm going to go through these in a little more detail.

The microbiology I'm sure you've heard about the last few days. These are some abbreviations that I use for MRSA, methasone resistant staph, and some of the Gram-negative rods that are resistant. And I'm going to talk a little bit at the end about clinical markers, which I think are very important for clinical trials and looking at response to therapy, CRP, C-reactor protein, procalcitonin. And I'll talk a little bit about clinical signs and a CPIS score.

So this is the idea, assay, logo, trying to get better drugs because we're facing more and more multi-drug-resistant pathogens. So my goals for this morning are really talking about enrollment, to extend the time that people are on prior antibiotics. We just finished a study of 250 ventilated patients. About 83 percent of the people were on antibiotics...
when they were enrolled in the study 48 hours later.

So if you want to exclude 83 percent of the patients, it's going to be very hard to get a clinical trial. I don't think we're different than most other hospitals.

A little bit about sputum microbiology. I think quantitative cultures are absolutely important, because virtually every intubated patient will have a bacterial culture that's positive. So we have to look at a number; I'm going to talk about numbers. And then for outcome, I think mortality is an important outcome, but also looking at clinical endpoints, which we do every day in the intensive care unit. It's very important to look at response to therapy and the efficacy of antibiotics.

Finally, I want to plead with you that VAP, where we have cultures on virtually every patient, we know what the pathogens are before we start them or enter them into clinical trial, is applicable to VAP and that basically the same pathogens that cause HAP also apply to VAP.

Here's a schematic of the lung. This large
arrow at the top here is basically -- the primary way
that bacteria get into the lung is through the
oropharynx. The oropharynx has about a thousand to a
hundred thousand times as many bacteria. When they
go into the lung, they colonize the trachea, then the
trachea bronchioles, and down here. And finally when
we have pneumonia, we have two entities here. The
first entity is tracheal bronchitis, meaning that the
infection is in the tracheobronchial tree, and then
ventilator-associated pneumonia or hospital-acquired
pneumonia, which means that we have lung parenchyma
involvement.

Now, there's only really one way into the
lung. Everybody aspirates every day. Bacteria, once
a person is intubated, enter the lower airway, so
there will be positive cultures. When you put an
endotracheal tube in and put up the balloon,
basically, that person can't cough or get bacteria
out of the lower airway. There's leakage around the
tube. So the colonization is extremely common in
ventilated patients.

Now, here are the bacteria shown here.
These bacteria on the left are common bacteria that we don't call multi-drug-resistant. It's the same for HAP, VAP, and ventilator-associated tracheobronchitis. These are non-multi-drug-resistant pathogens that are commonly isolated. On the right-hand side are the multi-drug resistant pathogens that we're seeing methasone-resistant staph aeruginosa, pseudomonas. I'm sure you've heard these many times over the last couple days: multi-drug-resistant, antibiotic-resistant Gram-negative rods that have a variety of names, acineta outbreaks markedly increasing in the United States, highly resistant organism, and stenotrophomonas.

Here is some data just on VAP, because I'm going to focus primarily on VAP, because I think we can extrapolate what we learn from VAP to HAP. And basically, these are the sickest patients in the hospital. They have an endotracheal tube in place. They're connected to a ventilator. Once you put that endotracheal tube in a patient's trachea, they increase the risk of pneumonia 6 to 21-fold. And basically, when we look at antibiotic use in the
hospital or in the ICU, about 50 percent of the antibiotics that are prescribed are usually to treat respiratory infections.

The crude mortality rate for this population is about 20 to 40 percent. Morbidity is huge. Short-term and long-term morbidity is huge, so it's important to try to manage these patients appropriately earlier. And the cost per case is about 15 to $40,000 per patient.

Also, if you can see in this patient, with this patient, it's very hard to get an informed consent from a patient like this. These patients are sedated, they're intubated. We have to work with family members. In studies we've done, we've sometimes had to interview 500 people to enroll 100 people in a clinical trial in a critical care unit. So keep that in mind.

Now, here is what we have. Nasopharyngeal colonization. All of us have millions of bacteria in our oropharynx. Basically, the bacteria leak around the endotracheal tube or aspirate into the lower airway. Everyone in this room aspirates every day
and bacteria gets into our lower airway, but we don't get pneumonia.

So it depends on the pathogens, the bacteria that we actually aspirate, the numbers, the type, and the virulence of the bacteria, and we don't know lots about these entities. We just know about what their names are. Then we have lung defenses, the cilia, the humoral antibodies, and the cellular host defenses, that when bacteria get down there, are able to control the infection.

This is what I call the war zone. Virtually everybody who has an endotracheal tube in place at 48 hours will have tracheobronchial colonization. We'll be able to isolate a pathogen in the lower airway. Some of these patients will go along and develop tracheobronchitis, just involving the tracheobronchial tree, and a smaller number of people will have VAP. And I'm going to try to convince you today that these entities, ventilator-associated tracheobronchitis and VAP, are intimately linked.

So I'm going to talk a little bit about the pathogenesis today. I'm going to talk about
diagnostic criteria, and it's important to include two entities in this; one, the clinical criteria, which is important, and the microbiologic criteria. So you can have microbiologic criteria, but without both of these, it's hard to make a diagnosis of VAP.

The outcome should be mortality, but, also, clinical outcomes in response to therapy is very important and gives us a lot of information about how effective a therapy is, and I'll talk a little bit at the end about biomarkers.

So a little bit about microbiologic and clinical data. What do we know? First of all, we have to look at sensitivity to be able to diagnose pneumonia if it occurs and basically to be sure, if we get an isolate, that the diagnosis does confirm pneumonia. Unfortunately, there's no gold standard for diagnosing HAP and VAP, and that's one of the problems I'm going to talk about.

So here's the sequence as far as a schematic of an intubated patient. Here is the upper airway. So this is what we call ventilator-associated tracheobronchitis. So we're talking about not
isolating any bacteria, basically. Usually, the bacteria that's initially isolated is the one that becomes significant. So we're looking at a hundred thousand to a million bacteria per ml of sputum. These are not small numbers, a hundred thousand to a million. This correlates very well with semi-quantitative cultures that are done in many hospitals, including our own.

Some individuals, this would tell us about tracheobronchitis and VAP, because we're sampling down in this part of the airway here. When we do bronchoalveolar lavage, we basically are putting the catheter down, a plugged catheter, putting some saline down, and then pulling back to get a sample out in the periphery where the lung parenchyma is.

The definition of VAP is to have a bronchoalveolar lavage culture with over 10,000 -- not just having a positive culture, but having over 10,000 organisms per ml of fluid aspirated.

So I want to just talk about these two entities, because I think they overlap and they can
be very difficult to tell apart from each other. So
temperature, white count and sputum, same for VAP and
tracheobronchitis. Pathogens, exactly the same,
what's causing tracheobronchitis is the same thing
that's causing pneumonia. The difference is that you
have to have an infiltrate on chest x-ray to make a
diagnosis of VAP, whereas, basically, the chest x-ray
is clear or you can't determine if there's a new
infiltrate, that would be VAT.

Quantitative microbiology, exactly the same.
A tracheal aspirate, the microbiology is exactly the
same; not just having a pathogen, but having a
quantitative culture that meets these criteria.
Semi-quantitative growth, more than 3 to 4-plus would
be significant. And if you're using BAL, we would
use the standard definition, which is 10,000
organisms per ml.

So here are the standards for using
pneumonia. We could use these two, that if you get a
positive culture by BAL or protected specimen brush,
we would expect these two criteria, and these are
accepted criteria internationally.
If we're looking at tracheobronchitis and pneumonia and we're not doing BAL, because many hospitals do not do routine BAL, basically, you can use quantitative cultures here or semi-quantitative cultures, and these correlate very well, as I'll show you in a few slides.

Now, if we were here 20 years ago, we would be asking the same question, how do we diagnose a urinary tract infection, because we don't have a universal accepted criteria. So, basically, Ed Kass, in 1955, said that we can't just treat every bacterial culture of the urine that we get in the hospital. We have to have over a hundred thousand organisms per ml. There was a big fight. Should it be a hundred thousand or 10,000? Ed Kass won; it was a hundred thousand. That's the standard we use in every hospital throughout the United States and Europe, a hundred thousand. But you have to have urinary tract symptoms, you have to have pyuria, meaning that there's white cells in the urine indicating infection, and you have to have a positive urine culture.
Now, if we have a lot of bacteria, particularly in women in the vaginal vault, there's millions of bacteria. The bacteria go into the bladder, and this is cystitis. We say 10-to-the-5th, a hundred thousand organisms per ml, that's the diagnosis of cystitis. If they've got kidney disease, back pain, fever, sepsis, hives, we say that they have kidney infection or pyelonephritis. Again, the colony count is the same.

Now, when I think about the urine, the bacteria down here, they go to the bladder, and then some of them will go back upwards into the kidneys and cause kidney infection and secondary blood stream infection. And when you think about the lung, the lung starts here, and this would be what we would call tracheobronchitis, and this is what we would call pneumonia, lung disease, or parenchymal disease. So you could almost turn this upside down and it would be the same story.

So here's a randomized trial of ventilator-associated tracheobronchitis. I actually reviewed this article and wrote an editorial for it. And,
actually, I thought I was pretty knowledgeable about this, but it was a shocker for me, and I thought the data were very impressive; randomized clinical trial of antibiotic therapy for ventilator-associated tracheobronchitis. The definition was a million organisms per ml of sputum. That was the definition to get in, plus clinical symptoms.

They randomized the patients to either have early therapy or delayed therapy. The people that got antibiotic therapy, where the diagnosis of VAT was made, 14 percent went on to develop VAP at a later time; 47 of the people that did not get antibiotic therapy developed VAP. The mortality was significantly worse in the people that had delayed antibiotic therapy, and ventilator-free days was worse. The longer you keep a person on a ventilator or the tube in place, the greater the risk, the poorer the outcome.

So a little bit about key points for clinical trials. The natural history -- I'm going to show you what the natural history of colonization is in patients that are ventilated. The diagnosis
requires microbiology plus clinical criteria. I'm going to try to show you that I think that is usually a precursor that occurs before you develop VAP; that VAP patients are associated with poorer outcomes apropos to this study I just showed you, the randomized clinical trial; that these two may overlap, because sometimes it's virtually impossible to tell them apart without a BAL or a PSV; and that, basically, I think VAT would be a very important target for clinical trials and to look at the efficacy of antibiotics.

Why? We're looking at a bacterial load of a hundred thousand to a million organisms per ml of sputum. And when antibiotics are started, they don't go from a million, to a hundred thousand, to zero. They go down to 10-to-the-4th and maybe 10-to-the-3rd. So we're looking at log drops in bacteria.

Next slide. So this is a natural history study that we just finished at our hospital, 188 consecutive patients that were ventilated more than 48 hours. Basically, we looked at heavy colonization, we looked at a hundred thousand, and we
looked at a million organisms per ml to see what the incidence. About 40 percent of the people met this criteria; less if we use the higher cutoff.

People that went on to VAT, about 23 percent of them developed tracheobronchitis, by the definition I discussed previously. And of the people that developed VAT, a smaller proportion of these went on and developed ventilator-associated pneumonia, about 7 percent, 5 to 8 percent, depending on what clinical criteria we used. And, basically, there was good correlation between quantitative and semi-quantitative cultures.

Now, this study was done independently. Cultures were collected every day on the patient, data was collected, but the information was not given back to clinicians. Basically, the clinicians in our unit do a diagnosis by BAL. They did BAL in 51 of the 188 patients; 13 of them were positive for about a 7 percent rate of what we would call VAP, which correlated actually pretty well with the outcomes that we got using semi-quantitative cultures or quantitative endotracheal aspirates, i.e., no BAL.
So there was actually good correlation here.

This is the natural history of what happens in a person after 48 hours of colonization. They enter the study here and, basically, the colonization rate goes up here. But a smaller portion of them will develop criteria for VAT, that's microbiological and clinical criteria, and then a smaller number here. This is at 10-to-the-5th and this is at 10-to-the-6th. So it shows you exactly what happened.

Virtually everyone that's in this group had VAT before they actually went on and developed VAP.

We looked at outcomes. People that had heavy colonization, these are looking here at hospital days shown here on the left, ICU days shown in the middle, and ventilator days. And the outcomes of people that had heavy colonization was worse than people that didn't have that. People that had VAT had more hospital days, more ICU days, and more ventilator days. These are all bad outcomes. You want to try to get the tube out and get them off the ventilator as soon as possible. And for VAP, basically, there was little difference, but the
numbers of patients in each of the groups was small, so this is probably a size effect.

So I'm going to try to show you that these data suggest that VAT is a clinical diseases. VAT is a precursor to VAP. It's associated with poorer outcomes and, basically, treating it, at least in one randomized study, was able to decrease progression to VAP, which I think is what our goal should be. And I think it would be a very good target for seeing the effect of antibiotic therapy in clinical trials.

Also, when you look at this and we have an intubated patient, you have access to the lower airway, you know what the bacteria is, you know what the colony count is. And just like we do in test tubes, when we put antibiotics in with different concentrations of bacteria, we look at kill curves.

So this would be staph aureus. Here is a different antibiotic. Antibiotic A, rapid kill in a very short period of time, three hours. Here's an antibiotic B which has a kill that's good, but it takes a longer period of time. Then there are certain controls here. Obviously, it continues to
grow, and no antibiotics in this group, or
antibiotics that wouldn't be effective would go along
these lines.

So when we're looking at trying to determine
efficacy of antibiotic A versus antibiotic B, we have
basically a host where we can get bacterial samples
and look at killing counts over time, because we're
starting with a million to a hundred thousand
organisms per ml in vivo. This is in vitro, but we
have actually an in vivo model that we could look at
the efficacy of antibiotic A versus antibiotic B.

So a little bit about mortality. I think we
can look at 14 and 20-day mortality. Mortality is
going to be in every clinical trial. But the
clinical response to therapy is something we do every
day in the intensive care unit when we start therapy,
and we want to look at clinical outcomes and response
in addition to mortality.

Biomarkers, we don't use biomarkers at our
institution, but for a clinical trial I think they're
very important, because they supplement some of the
observation data that we are going to be collecting
in the top two here. And then I'm not going to go
into this. There's a lot of good data looking at
pharmacology modeling, and I think it's very
important before you start a clinical trial.

Now, I've used this just as an example about
how you don't necessarily have to look at mortality,
but you can look at lots of outcomes. This is a
randomized clinical trial that changed what we do in
the intensive care unit every day. It was done by
Jean Chastre. It was in JAMA 2003. And, basically,
it looked at people that were randomized to 7 to 8
days of therapy versus 14 to 15 days of therapy, and
they looked what the outcomes were.

Before this trial, we were often treating 14
to 15 days of therapy or longer, and, basically,
these are Kaplan-Meier plots of survival, and you can
see 8-day versus 15-day. This is 7 versus 14. The
French have sort of a strange way of looking at their
week. It's either 7 to 8 days or 14 to 15 days. But
you can see here that these plots are virtually
superimposed, and this led, in addition to other
studies, to the recommendation to shorten the
duration of therapy.

The previous studies had actually looked at temperature response. So looking at temperature response, virtually no difference in the groups. They defervesced at the same time. Leukocyte counts were very similar. Oxygenation was very parallel. These are all endpoints that it would be important to monitor. But we can also look at CRP, procalcitonin, and the CPIS scores. These are other targets that have also been looking at response to therapy.

So here are the recommendations. Accept prior antibiotics for a longer period of time. In our study, at 48 hours, 83 percent of the people were on antibiotics at 48 hours when they entered the natural history study. These people are sick. They've got other infections. They're going to need antibiotics. So to try to find someone that's not on antibiotics, you're going to be eliminating a lot of people from the trial.

Quantitative microbiology. You can't just take any culture you get. Most hospitals use quantitative or semi-quantitative. Our data show
that basically these outcomes, whether it's semi-
quantitative or quantitative, for endotracheal,
aspirates are the same. Many hospitals use BAL or
PSB, as well.

So the outcome should include mortality. I
think clinical response is extremely important to
monitor for efficacy of antibiotic A versus
antibiotic B. The bacterial load in vivo and
actually in vitro also looks at how effective an
antibiotic is for eliminating some of these multi-
drug-resistant organisms.

Now, the nice thing also about VAP is that
when you culture that person on day 2 or day 3, the
pseudomonas that you see on day 2 or day 3 are
usually the same pseudomonas that's there on days 5,
6 and 7. So that you know, rather than starting
broad spectrum antibiotic therapy and de-escalating,
you can use what's called targeted therapy for an
antibiotic trial, and you would know whether the
organism would be an organism that would be an
important organism to evaluate in the trial.

So, basically, load, ICU days, hospital
days, outcomes markers, I think, are very important. If you can get the tube out and get the person out of the intensive care unit, that's a good outcome.

I'm strongly in favor of serologic and biologic markers for clinical trials, and, also, relapse rates are very important to make sure that the antibiotics, when they're effective, that the relapse rates aren't different between antibiotic A and antibiotic B.

So I've tried to convince you today at least my belief is that we're waiting too long to treat therapy for VAP and that VAP and VAT overlap, and that this would be a good model for evaluating not only antibiotics, but also some of the prevention strategies that we're using in the intensive care unit to prevent pneumonia.

So, in summary, microbiology I think is actually key, particularly for looking at antibiotic A versus antibiotic B. Basically, VAP and VAT overlap, but I think that both of these entities would be clinical entities that would be valuable to look at in the clinical trial of
antibiotics.

The antibiotic endpoints should be mortality plus the other things that I've talked about. I think the focus should be on VAP, because we get microbiology in every patient. In HAP, we may or may not know exactly what's causing the pneumonia. I think we can extrapolate that if an antibiotic is effective against VAP, I believe it's going to be effective against HAP, too, since the pathogens overlap. And I think good modeling is important.

Finally, to have a good clinical trials model like we have for the ACTG, where multiple sites are enrolling patients, we have independent data analysis, and that people are able to look at data independent of having lots of small studies that are analyzed by different people with different interpretations.

So this is sort of how I think where we are with clinical trials in VAT and VAP. Now, the future antibiotic trials for HAP and VAP, if you keep doing the same thing, you'll keep getting the same results. We're going to be in the same predicament, no bugs,
no drugs. If you want to do better, we have to try
something new and try to improve the way we're doing
clinical trials.

I love this quote from Oliver Wendell
Holmes, "Man's mind stretched by a new idea, never
regains its original dimensions." I hope that's
ture. If this was your mind before we started today,
I hope that it looks like this after the
presentation.

Thanks very much.

DR. MOORE: Thank you very much, Dr. Craven.
Let's proceed now with Dr. File's
presentation.

Dr. Craven, was that a picture of a healthy
brain or a diseased brain? I'm just curious.

[Laughter.]

Guest Speaker Presentation - Thomas File

DR. FILE: Thank you, Dr. Moore. As I said
yesterday, again, it's a pleasure to be here. Let me
again say that I'm an infectious disease clinician.
I'm not an intensivist. I'm not a critical care
physician. But I will stay that I spend a large
segment of my time in the intensive care unit, primarily trying to stop antibiotics, actually, but doing a lot of de-escalation.

However, to prepare for this presentation, I did confer with a lot of my intensivist critical care colleagues, many of them, actually most of them, who participated in the workshop in 2009. So you will see that in my presentation I may be giving some quotes from some of them.

As was alluded to yesterday, I think the need for new drugs, new agents to treat hospital-acquired pneumonia, ventilator-associated pneumonia is much greater, is much more urgently needed than for community-acquired pneumonia. But we do need it for community-acquired pneumonia, as well, for issues that were discussed.

But we really have a clinical crisis here. I mean, all of us I'm sure, that are clinicians, have managed patients for whom cultures have been obtained for pathogens which are resistant to every one of the drugs that are tested, including even colistin. These could be pseudomonas, acinetobacter, or
stenotrophomonas. And so it is a real need that we have agents to try to address these types of problems.

Now, as we're all aware -- and, of course, the FDA, you're very aware of this because of the comments you've received -- that many companies are potentially withdrawing looking at some of these new agents due to uncertainty of the guidance.

Interestingly, again, two weeks ago at the annual IDSA meeting, Helen Boucher presented an abstract looking at new agents which may be effective against some of these multi-drug-resistant Gram-negative bacilli that are in early development. None of them, I don't think, were even in phase 2 development. But none of them had been planned to look at HABP and VABP because of the complexity and the concerns of the guidance. And so it is important that we have flexible, feasible clinical study guidance. And so I appreciate very much being able to participate in this process.

I think we're going to require, as Don just mentioned, innovative approaches. It certainly
cannot be business as usual because of the issue of the significance of these infections and the uniqueness of some of these pathogens. However, it's going to have to reflect standard of care and guideline principles in order to be relevant to the investigators and to our clinicians. And patient safety has to be optimal, and I think this is going to require individualized care.

It's difficult to generalize to any one specific regimen as a comparator. I mean, we're all aware of these super-bugs. They're all around. When we heard about this a couple years ago, about the New Delhi beta lactamase producing Gram-negative bacilli, we were very concerned. But it is in our country now, as well. It's basically global. And this is the type of patients we see when I'm in the intensive care unit, a patient who's been on the ventilator for 21 days, had a post-op infection, was septic postoperatively, and so was obviously on antibiotics for an intra-abdominal infection. We know that there's MDR or multiple drug-resistant pathogens in our ICU. He now develops a new fever, new pulmonary
infiltrates. He has an NG tube in. He's got fever, expectorate and sputum. And so one of the questions is does he truly have pneumonia. We'll discuss this very briefly, what diagnostic studies and what therapy, because this is all relevant to clinical trials.

I bring this up -- this is sort of a review that Mike Niederman just published looking at the de-escalation process for patients with ventilator-associated pneumonia, and he reviewed, I guess, eight studies here. And if you look at this, virtually every one of the studies, where there was de-escalation done -- and it's more than just de-escalation. I'm going to call it optimization, because that's what I do in the intensive care unit. On day 2 or day 3, when we have an isolated pathogen, we not only de-escalate, we oftentimes optimize, because we now know what the MIC is, and we're going to give different doses of drugs, we're going to specify drugs.

But this is extremely important as far as individualization of care, because if you look at
these studies here, the patients who had appropriate
de-escalation -- and I'm going to also say
optimization, because when we look at some of these
studies, it was more than just de-escalation, more
than just stopping concomitant adjunctive therapy.
It was also making sure that the drug that was used
was adequate in its dose, in its
administration -- that those patients that had this
de-escalation had a lower mortality rate. Now,
sometimes it's not significant, but in most of the
studies, there is a drop, and in some of them it was
significance.

So I think this illustrates one of the
issues. We have to be flexible here and we
can't -- it's somewhat different than community-
acquired pneumonia, where I think we can identify a
comparator and use that comparator for the entire
dosing of that particular study. I think it's going
to be difficult here, because we may have to allow
for some flexibility when we do identify the
pathogen.

Here's another review paper that was just
published having to do with pseudomonas infections, and I'm just quoting here that "Although randomized control trials are ideal, logistic considerations for such a study are almost insurmountable, in part, because of the resistance issues." But he goes on to say -- Dr. Sun and others go on to say -- and, Victor, used part of this, as well. The obstacles include the large number of patients required to attain statistical power and the difficulty in establishing a definitive diagnosis.

So I want to go back to this issue, because in the 2009 workshop, I sort of presented how clinical guidelines from around the world addressed the issue of management of diagnosis and treatment. And I'm just showing you many quotes about the dilemma, the diagnostic dilemma. If you look at our ATS/IDSA guideline 2005 -- which, by the way, are being presently updated, and they need to be updated because there is such a significance change in the pathogens and how we treat these very serious infections since 2005. But nevertheless, you can see that we stated back then that the diagnosis of
hospital-acquired pneumonia is difficult. The specificity of the diagnosis is undetermined.

I'm not going to show all these quotes. Let me just go down to the bottom, from the Cochrane review from a couple years ago, that VAP represents a great challenge to clinical practice and has triggered numerous discussions regarding the best diagnostic approach.

Now, at the 2009 workshop, I sort of compiled all of the recommendations from the practice guidelines from professional societies that were global, and, basically, these are the results of that; that the diagnosis as recommended for patients with VABP or HABP for which clinical trials would be appropriate would be based on basically clinical findings of a new infiltrate plus two of the following: fever, leukocytosis, and purulence.

Now, as I look at the guidance, I think you mention all three of these are required. But, also, if I look at the position paper, at the result of that workshop that was published subsequently in Clinical Infectious Diseases last year -- or at
least -- I think it was last year, maybe in
2009 -- the recommendation by the societies who
participated in that workshop was that exactly this
would be the clinical criteria; that is, you only
would require two of those three clinical parameters;
that microbiologic information should be obtained,
and there was a lot of debate, as Dr. Toerner said,
about should it be quantitative, should it be BAL,
should it be invasive, should it just be under
tracheal aspirates, expectorate sputum.

The consensus of the guidelines was it
doesn't matter. Just get some type of specimen and
then assess the appropriateness based on the Gram
stain. And then as far as therapy, at least as far
as the guidelines were concerned, stratified by risk
factors, and that you would need multiple combination
of antimicrobial agents for high risk patients.

Now, this is where I think our guideline
needs to be changed, because if you look at our 2005
guideline, we address patients, for example, with
healthcare-associated pneumonia. I know we're not
talking about that, but we sort of generalize all of
these patients on a risk for MDR, when it's quite apparent now from more recent studies that that is not necessarily true.

Then many of you may be aware of a paper that was presented earlier this year that was quite a bit controversial, I think, as far as its response, a paper by Kett, et al, which suggested that patients who were treated according to our guidelines had a higher mortality rate for ventilator-associated pneumonia than if they were treated by individual assessment by the treating physician.

I think basically what this means is that if you know what your pathogens are in your institution, you're going to be much better at giving empiric antimicrobial agents than just blindly following a guideline. By that I mean -- because we don't have in our guidelines give empiric colistin or use antibiotics somewhat differently. But if you know what's in your intensive care unit, I think you're going to be much better at being able to give initial empiric antimicrobial agents.

Now, if we look at our guidelines, and since
Don mentioned this, as well, there was sort of a
difference in the relationship to which the CPIS or
biomarkers were assessed. So as far as the
considerations for this meeting, I'm going to address
primarily the efficacy of all-cause mortality, at
least as it is seen in randomized clinical trials,
and basically the use of prior antimicrobial therapy.

So mortality, as it has already been
addressed, is the primary endpoint. But the question
is how much is truly seen in randomized clinical
trials. I'm looking at a review paper here that was
published about three years ago of 41 trials, 7,000
patients, where the overall mortality was 20 percent,
and that's what your goal is. Right?

But it's interesting. If you look at those
studies critically, of these 41 studies, most of them
were published in the '80s and '90s, actually. Only
12 were published after 2000, and none -- well, I
guess only one after 2005.

So if you look at more recently published
trials or randomized clinical assessments in
ventilator-associated pneumonia -- I'm showing some
of these. So the doripenem and imipenem, Dr. Floyd already mentioned this, but I think it's important, again, to reinforce. And I'm just going to quote that they found that "the 28-day mortality rate was substantially lower" -- it was 10.8 percent, the doripenem arm, 9.5 percent, the imipenem arm -- "than what you see in the observational trials or the epidemiologic trials that have been used to determine the all-cause mortality."

This may do -- as we all are all aware -- we discussed this yesterday -- with even the CAP trials. Due to the impact of the stringent inclusion/exclusion criteria that exclude unstable patients with acute respiratory distress syndrome, septic shock, severe renal disease or dialysis, or immediately life-threatening, and, particularly, as Don even mentioned, the difficulty in getting consent from these patients or these patients' families.

So that's that study. The linezolid vancomycin trial, which was reported last year at IDSA, if you look at the 28-day all-cause mortality at the end here, it's 13.6 percent. And
interestingly, in a report presented at IDSA just two weeks ago, a group looked at the mortality here and found that the APACHE-II and another scoring system, IBMP -- it's sort of like the CURB-65. I is immunosuppression, B is blood pressure, M is multilobar infiltrates, P is low platelets, and 10 is in the hospital 10 days or more. But, anyway, they found in an independent assessment that that could potentially predict mortality. But they found that in the study looking at it, they were not good tools for severity of disease. They did find, however, that age was, at least for 14-day mortality.

About the tigecycline imipenem trial, which was presented, I think, at the 2007 ITGAC, the tigecycline mortality was 19 percent, but the control was only 11.5 percent. And then the televancin, which was just published this year -- and I apologize. If you look at my handout, there was a mistake there, but it's corrected on the slide. The mortality did achieve approximately what you want, about 20 percent.

But if you put all these together, I think
the mortality, again, in a randomized control trial as opposed to patients in observational trials is going to be less, oftentimes, than 20 percent.

As I said yesterday, mortality clinical outcome is going to be multifactorial. It's going to rely more than just on the antibiotic and the bug. It's going to rely on the host factors, genetics, underlying diseases, et cetera. And, again, discussing with many of my intensive care colleagues, most intensive care patients don't die directly of sepsis; often from withdrawal of care. We've become very good -- this is a quote -- "We've become very good at keeping patients alive in the ICU." Early mortality will never even approach 15 percent. Late assessment is a disconnect between antibiotic treatment and mortality, because all of the other -- well, I won't say confounding, because Dr. Floyd said I shouldn't say confounding, but all the other issues that are involved in what happens to patients when on the ventilator for over two weeks.

Don mentioned other outcomes. And I was impressed by what Dr. Calhoun said yesterday in his
very elegant remarks about oxygenation with patients who had pneumonia, and I think that's true. If we look at least at a CPIS score -- this is one study from Luna and others, and other studies have shown this, as well, that if you follow the CPIS score, and this is looking at day number 3, you can see a significant drop in patients who survived versus those who did not survive, and it was significant. But the biggest parameter that was most strongly associated with eventual survival was oxygenation. So if you look at the PaO2/FIO2 ratio -- and, again, this is day 3 post-therapy. Survivors had a much -- I guess we're up here -- had a much better PaO2/FIO2 ratio than non-survivors.

Then, again, this was just recently published at -- or presented at ITGAC -- to IDSA -- I apologize -- two weeks ago by Ethan Rubenstein, again, looking at the linezolid versus vancomycin trial, showing that by day 3, although it wasn't statistically significant, there appeared to be some difference in oxygenation of these patients, at least based on hypoxemia.
What about procalcitonin? There was a lot of issue about procalcitonin yesterday. In due respect, I do feel that procalcitonin is better, at least in the sed rate or the C reactor protein that was mentioned yesterday, because, indeed, it is a response directly from cytokines from bacterial infection. So I think at last from the standpoint of differentiating bacterial infections from other inflammatory processes, it is more discriminatory than perhaps C reactor protein.

But at any rate, here's a study by the Paris Group, Jean Chastre's group, looking at procalcitonin over days in patients that had ventilator-associated pneumonia, and they found that the levels did decrease during clinical course of VAP, but were significantly higher from day 1 to day 7 in patients with unfavorable outcomes.

So maybe this can also be an inflammatory marker, a biomarker that may be useful in clinical outcomes. And based on these data, procalcitonin could be a prognostic marker of outcome during VAP. But I realize that it's not as clean in VAP as I
think it is in community-acquired pneumonia because of other issues that patients have in the intensive care unit.

Now, Don mentioned this issue -- I know this is not well defined or validated -- about following patients microbiologically, quantitatively, after initiating antimicrobial therapy. This is actually a study that was done in 1993, and it includes CAP and nosocomial pneumonia, so it's not generalizable for necessarily ventilator-associated pneumonia. But all these patients were on the ventilator. Either they had severe CAP requiring mechanical ventilation or they actually had nosocomial pneumonia.

But, again, if you look at the responders, they had a drop in their so-called bacterial load much more quickly -- well, as opposed to the non-responders who did not. So, again, it's a reflection of the sort of effect of the antimicrobial agent. And, by the way, when we give an antimicrobial agent, this is what we want. We want that antimicrobial agent to reduce the pathogen, and we hope that will translate into clinical improvement of the patient,
although I know that that's not always very
correlative.

So what about prior antimicrobial agents?
Well, when I discussed this with my ICU colleagues,
it's almost what Don said. If you exclude prior
antimicrobial agents, this is absolutely a
nonstarter. They cannot do clinical trials in the
ICU for ventilator-associated pneumonia. Why?
Because the majority of the patients that develop
ventilator-associated pneumonia, just like the
patient I showed you who actually was on antibiotics
for intra-abdominal sepsis and now develops a
pneumonia, are going to be on antibiotics.

We also know, as has already been mentioned,
that patient outcomes are affected by early therapy.
If you look at sepsis studies, a one-hour delay
increases mortality by 7 percent. So we want to get
antibiotics early. Most patients, as I already
mentioned, in the ICU are on prior antibiotics.

Now, if you look at studies -- and this may
seem discordant with what I just mentioned -- but if
you look at studies that serially follow patients who
are on antimicrobial therapy, at least early
evaluation does not show that you're going to
eradicate the pathogens associated with VAP
significantly at all, and this has been shown in both
MRSA and in Gram-negative bacilli in patients who
have had serial BALs.

Interestingly, you do show that you reduce
some of the other pathogens, such as pneumococcus and
haemophilus very quickly, but not so much these
pathogens. And some studies have actually shown that
the mortality is actually higher in patients who were
on prior therapy. So if you want to enrich for
higher mortality, enroll patients who are already on
antibiotic therapy.

So what about the number of trials? Well,
they must be feasible. If too restrictive, we'll
never be able to recruit the number of meaningful
patients. Consider one VAP trial with support from
pharmacokinetics, pharmacodynamic data and other
indications, and maybe even consider HCAP admitted to
the ICU on the ventilator.

In a presentation that we actually gave two
weeks ago at IDSA, we looked at patients who had the traditional definition of HCAP. Most of them came from extended care facilities, but required admission to the ICU. And if you look at that versus the HABP/VABP, there was no difference in the microbiology.

If we looked at MDR pathogens, there was no difference. These patients had just as much MDR as the traditional HABP/VABP. So I think we can enrich perhaps patients who have this that require admission to the ICU and are ventilated.

So as far as the comparator, I think this is going to require innovative thinking. I doubt that we can use one regimen. There's variable multiple drug resistant patterns at different sites. We're going to have to consider individual optimal baseline therapy. And I know this is mentioned in the draft maybe more for the superiority trials, but we have to maybe specify how we're going to give patients what therapy even after initiating antimicrobial therapy and identifying other pathogens.

I say that because some of these newer anti-
Gram-negative agents, which look very promising to me and are just in the stage of going to Phase 2 trials may be somewhat selective in their activity. Some are very good against pseudomonas, but not good against acinetobacter or KPCs. On the other hand, some are good against KPCs and acinetobacter, but not pseudomonas. And so it's going to be somewhat difficult to put these in trials where we have to, at least initially -- unless we use molecular tests, which we mentioned yesterday for CAP, but are also available for some of these Gram-negative pathogens, to maybe identify acinetobacter, identify pseudomonas at least initially.

I mentioned yesterday some of the barriers in the clinical trials. Don mentioned these, as well. I think a bigger one here is going to be prior antibiotics, because we need early therapy. If we don't, it's associated with increased mortality if we delay therapy. So I think we're going to have to allow antimicrobial therapy particularly since most in the ICU are on prior antibiotics.

We mentioned yesterday about the consent
forms and how intimidating they are, and how time consuming they are, and how difficult it's going to be to obtain them -- Don mentioned this, as well -- in patients who are on ventilators or are too sick, and the family is too concerned to even be able to generalize the information in a 20-25 page consent form. It's really intimidating to them.

So I think we need well trained study staff, and I was really impressed with Dr. Neely said yesterday about in their pediatric trials, having a very short, one-page, simple consent form to at least get patients into the trials, and then they have time to look at maybe the more comprehensive consent form. But the other possibility is, as I mention here, to allow antibiotics while obtaining consent.

Study agents not active against all relevant pathogens and, as we mentioned, some of these are going to have selective activity. So we're going to have to allow adjunctive therapy. I just don't know how we're going to do this. Dr. Floyd mentioned the doripenem and Peptazol study, and he's right. Most of these patients were on adjunctive amikacin
therapy, which is potentially going to reduce the interpretation of the results. But if you have a patient who's got ventilator-associated pneumonia and you're using a drug like, let's say, doripenem in that study, in our setting, doripenem probably covers about 80 percent of the pathogens. Now, if we add an aminoglycoside, we get up to about 90 percent.

Now, it's not necessarily that we want to use an amikacin or aminoglycoside monotherapy, but that's what it really means for that extra 10 percent of coverage. And so IRBs I think are just going to not allow us to use monotherapy with these agents that may only cover 70 or 80 percent of the pathogens, at least initially.

This, I guess, is related to this next barrier, which is regimens limited by international availability. I think we're going to have to consider state-of-the-art comparison in specific sites; again, maybe then specify or optimize therapy once we get the results of the cultures.

Then it's already been mentioned by Dr. Toerner, as well, or maybe by Ed that we were
seeing reduced numbers of ventilator-associated pneumonias as we introduce these preventative measures to reduce them. Also, when I talk with my intensive care colleagues, they're much more efficient now at getting patients off of ventilators than they were even five years ago. And so we're going to reduce the number of ventilator-associated pneumonias.

When I go to our ICU, we have a big sign that says how many days since we've seen a ventilator-associated pneumonia, and the last one it said was 75 days. It's going to be difficult if we only see three or four a year now, where we used to see a lot more of that. Actually, a lot of that's because now we're diagnosing, as Don said, VAT rather than VAP.

But at any rate, what about our considerations here? Well, we have to have feasible studies. They need to be achievable by industry, but they also have to provide optimal care of patients. The 20 percent mortality may be too high for randomized clinical trials today, with advancement in
care. We need to allow prior antimicrobial therapy, may consider using molecular tests that might be able to identify early if this is an acinetobacter or pseudomonas, for which we would have selective therapy for those patients.

Endpoints, early and a 28-day time point needs to be considered. I guess I would favor the 28-day, but some of my colleagues would favor the 14-day, as I mentioned in my presentation. Consider both mortality and clinical outcomes, maybe microbiologic outcomes, as well. Again, I put a question mark behind the procalcitonin.

Consider using HCAP to enrich patients, because we're always going to have patients admitted from the long-care facilities with pneumonia to the intensive care unit. But we may need to have smaller studies, and maybe look at interim results. And if patients look like they're responding well and this drug looks good, there's going to be a clamor to start using this drug, maybe compassionate use, I don't know, but maybe have some type of assessment such as that.
We already said about the barriers, and Don already mentioned clinical trials networks, and we mentioned that yesterday. So with that, I'll conclude my presentation. Thanks for your attention.

DR. MOORE: Thank you, Dr. File, for that very thorough presentation.

We're supposed to take a break at 10:00, but I think -- if it's okay with everybody, I thought we'd do the last guest speaker presentation with Dr. Fromtling, representing PhRMA, squeeze that in, and then we'll take the break.

Guest Speaker Presentation - Robert Fromtling

DR. FROMTLING: Well, good morning, and thank you for the opportunity to discuss regulatory and clinical ideas with regard to the development of drugs for hospital-acquired and ventilator-associated bacterial pneumonia. And today I am representing PhRMA.

So let's begin with the first FDA question. Please discuss the merits and limitations of the single trial plus supportive information proposal for hospital-acquired and ventilator-associated bacterial
pneumonia, and please discuss the types of supportive
evidence that would be considered acceptable if only
a single trial is conducted.

So the PhRMA consensus view is that we agree
with FDA that one trial can be sufficient when paired
with data from another indication. However, we also
think that one trial alone could suffice in some
cases, and here's why.

If we look at the core requirements of the
Code of Federal Register, it says that reports of
adequate and well controlled clinical investigations
provide the primary basis for determining whether
there is substantial evidence to support the claims
of effectiveness for new drugs.

There are several important implications in
this. Preclinical data are usually insufficient
alone. Adequate and well controlled clinical data
are required. Confirmation via more than one trial
is desired -- thus the word "investigations" in the
CFR above -- but the FDA does have flexibility. And
it's mentioned that other confirmatory evidence may
be acceptable, at FDA's discretion, in support of an
adequate and well controlled trial.

So what might this mean for antibiotics? Do we really need two trials for every indication? We have to keep in mind that infection is unusually rich in nonclinical confirmatory data, or we can approach this differently by perhaps allowing for the uniquely powerful preclinical estimates of antibiotic efficacy, allowing for the fact that the way antibiotics work, that is, their pharmacological effect, is identical across all settings, and allowing for our ability to show exposure-response correlations from human studies that reproduce the exposure-response effects proven in animals.

So if we again look at the guidance, the usual requirement for more than one adequate and well controlled investigation reflects the need for independent substantiation of experimental results. A single clinical experimental finding of efficacy unsupported by other independent evidence has not usually been considered adequate scientific support.

So interestingly, the requirement is not replication of studies and there are options. There
are other possible paths and related diseases that
can have related endpoints.

    So if we look at independent substantiation,
two trials could work; trials in related diseases,
where the general purpose of therapy is similar. So
this is a reasonable start. One trial in each of two
indications should be seen as a very strong
registration package.

    What about one trial looking at multiple
endpoints from different events? That is, combining
pharmacological and pathophysiological endpoints with
clinical endpoints is permitted when pathophysiology
of disease and mechanism of action of therapy are
very well understood and when the linkage between the
pharmacological effect and the clinical outcome is
strong. So this has precedent and fits antibiotics
very nicely.

    So the proposed separation in the draft
guidance for HABP and VABP, the comments on this is
that this will reduce program feasibility. It's hard
enough to enroll one patient group, much less each
separately -- and we've heard this from several
speakers yesterday and today -- and the separate
studies approach is artificial. Both are bacterial
infections of the lung, both are managed in the same
way, and both are hospital based. For example, we do
group other infections. Appendicitis and colon
perforation are both part of complicated intra-
abdominal infection, and pyelonephritis and lower
urinary tract infection are both part of complicated
UTI.

So an appropriate balance would be permit
both in the same study. And as noted in the
backgrounder, there is an option proposed by FDA for
a single adequate and well controlled, non-inferior
R&D trial in ventilator-associated bacterial
pneumonia, in addition to supportive information that
will be adequate for an indication of both HABP and
VABP. This is certainly a significant step forward
and we welcome this idea.

It does come with some caveats, though. A
trial of this size that would be ventilator-
associated bacterial patients only would likely be in
excess of 900 patients. And as we just heard from

A Matter of Record
(301) 890-4188
Dr. File, this could be very difficult to enroll. So we would recommend a percent of VABP patients, supplemented by HABP patients, that would lead to an indication for nosocomial pneumonia, including ventilator-associated pneumonia, but we would modify this 25 percent that I have on this slide to 50 to 70 percent VABP patients. And we think that would be a realistic trial approach. In addition, the odds ratio metric would be the best approach for this type of analysis.

Now, if we look at the single trial and trial indication approaches, these are needed to permit flexible development. For example, a medically relevant package for a label making limited claims could consist of one adequate and well controlled study in one indication, plus consistent microbiological effect data in that indication, plus consistent exploratory microbiological and clinical data in other indications, plus supportive preclinical and clinical pharmacologic predictions. Other indications would require single additional studies.
The labeling would note the approval dataset, but also discuss the potential for activity against important types of resistant pathogens. The current understanding of the likelihood of activity beyond current indications should also be included. Many disease settings are not feasible to study and physicians are often forced to make educated guesses. So through the labeling process, let's try to make that as easy and informative to the treating physician as possible.

So if we now look at question 3, and, yes, this is out of order, please discuss the preferred timing for the all-cause mortality endpoint; would an assessment at an earlier time point be preferred to the 28-day assessment, the PhRMA consensus view is that if mortality is to be used, we think 28 days makes as much sense as anything else. But this does beg the question is mortality a good endpoint, and here's our thinking.

All-cause mortality has many limitations. A recent position paper endorsed by four societies emphasizes that limiting trials to a mortality-only
primary efficacy endpoint is not consistent with standard clinical practice. All-cause mortality is reduced by supportive care and increased by underlying disease. And fever, oxygenation and such are routinely assessed, so failure to consider these decreases clinical relevance and creates a risk that results of registrational studies will not extrapolate well to post-approval use. That means use in the real world once the medicine is approved.

So a suggestion. While all-cause mortality is a possible endpoint, clinical response based on clinical stabilization with survival may be more appropriate and relevant, because it better reflects the current medical practice and treatment scenarios, and clinical stabilization based on parameters similar to those used to evaluate ceftaroline for community-acquired bacterial pneumonia would be biologically and medically sound. And a supporting example such as arterial oxygenation changes we know are linked to mortality.

So we suggest mortality-plus. Mortality-plus is clinical stabilization with survival. It
would require survival for 28 days, require
physiological improvement without a change in
antibiotics. And this is really what the physician
wants to know.

This should give a success rate of around
70 percent, and with this success rate, we would now
think of an odds ratio-based margin of 1.714, which
really is the same as a 10 percent non-inferiority
margin at 80 percent success rate.

So now let's look at question number 2.
Please discuss if a non-inferiority margin of
10 percent will be acceptable if the active control
mortality rate is less than 20 percent. Please
discuss if the odds ratio or risk difference metric
is preferred when the control mortality rate is less
than 20 percent.

So the PhRMA consensus view is that at our
preferred endpoint of mortality-plus, we would select
an odds ratio margin of 1.71. If we must stay with
the less informative endpoint of mortality, we think
that agreed designs must tolerate a mortality rate as
low as 15 percent. In that case, we believe the risk
difference metric with a margin of 10 percent still applies at a mortality rate of 15 percent.

So with mortality-plus as the endpoint, the odds ratio margin of 1.714 is optimal, and we think the trial design should be similar to that of community-acquired bacterial pneumonia; that is, the odds ratio margin of 1.7, which is about 10 percent non-inferiority at 80 percent success in the ITT population, or an odds ratio margin of 2.15, equivalent to about a 15 percent non-inferiority at 80 percent success, in the microbiologically proven ITT.

So the resulting study at 90 percent power would require 336 patients per arm or 672 total for the ITT population; at 70 percent evaluable, the need to enroll 214 per arm to have enough for the microbiologically proven ITT at 90 percent power. So this approach has sufficient power and is a reasonable patient enrollment goal.

But if we really must use the endpoint of mortality, let's look at a 20 percent mortality rate. We still believe the design should be similar to that
for CAP, a margin of 10 percent for ITT population
and a margin of 15 percent for the microbiologically
proven ITT population. We would power assuming
20 percent mortality. Using risk difference for
margin would actually give a larger number of
patients per arm than 15 percent mortality, and we
believe that this requires 336 patients per arm or a
total of 672 for the ITT analysis, and we believe
that this could be feasible. With this study size
and a 20 percent mortality rate, at worst case, the
point estimate is minus 3.6 percent or 1.18-fold
increase. We'd have a less than or equal to 2.5
percent probability of a greater or equal to 1.5-fold
increase at a 10 percent margin.

Again, if we still are restricted to
mortality only, let's look at a 15 percent mortality
rate. And with the study size on the previous slide,
our worst case, the point estimate would be minus
4.2 percent or 1.28-fold increase, again, with a less
than or equal to 2.5 percent probability of a
1.67-fold increase at 10 percent margin.

For the microbiologically proven ITT
confirmatory analysis, at 70 percent microbiologically proven, the study is overpowered for 15 percent margin. The current N is adequate actually for 12 percent margin at 90 percent power. But we must take all the data together. Within the bounds of all other approximations we have used, the hypothetical 17 percent difference, which is really the difference between the 1.5 and the 1.67-fold increase in the failure rate, is well within the overall error of the method. The microbiologically proven ITT provides further support, as do other supportive data and other trials.

However, there is an elephant in the room. The FDA has assumed 70 percent rates of microbiology proof, and this is true perhaps for Gram-negative organisms. But two important narrow spectrum cases are now rendered inaccessible, staphylococcus aureus and pseudomonas aeruginosa. At rates of 25 percent for staph and 10 percent for pseudomonas, agents limited to these pathogens would require trial sizes three to sevenfold larger than those already discussed, and, quite honestly, the sample sizes are
staggering. A pseudomonas aeruginosa focused program would require 2900 patients per arm to prove non-inferiority at an odds ratio margin of 1.71. So to develop an antibiotic that's focused on one pathogen would be extremely difficult.

We look at the last two questions. Should a patient who develops HABP/VABP or receiving antibacterial drugs for other infections be enrolled in a HABP/VABP trial; and, if so, please discuss some scenarios where this will be acceptable? And if empiric antibacterial treatment for HABP and VABP has begun prior to enrollment in the trial, what duration of therapy would be acceptable and unlikely to confound interpretation of the treatment effect of the study drug? And please describe your rationale and what other information might be useful to address this question.

So the case of prior antibiotics, if a patient develops a hospital-acquired or ventilator-associated bacterial pneumonia while on something else, the prior something else can be ignored. That medicine is not working. Brief courses of other
empirical therapy area, we believe that permitting 24 hours of other empirical therapy is essential to successful recruitment. Without this proviso, we believe that the regulatory and clinical hurdles would be so high that antibiotics for HABP and VABP may not be developed. This again has to do with size of trials, feasibility of enrolling patient numbers in a reasonable timeframe.

We also think that such patients are part of the standard usage patterns for any new drug. If you exclude those with prior empirical therapy, you'll likely exclude critical subsets, such as the most seriously ill. Again we've heard that from our speakers earlier today. Furthermore, prior therapy would be expected to have uniform effect in all treatment arms; thus, the clinical trial should still yield conclusive results.

If we look at other issues, such as microbiology and the safety database, with regard to microbiology and breakpoints, although the focus programs being discussed today will enable progression of drug candidates, the smaller programs
will lead to lesser numbers of microbiologically proven cases. There will likely be few or no cases at the population MIC-90. However, we must not lead to setting the breakpoint at MIC-50. We certainly do not want to move in that direction. And as was discussed yesterday, it's critical to use clinical data, population MIC distributions, and PK/PD data to help establish and set breakpoints.

Now, with regard to the safety database, all prior comments have focused just on efficacy. We certainly cannot ignore safety in the development of these new medicines. So it's a given that the overall program must accrue sufficient experience to give a reasonable view of the safety profile or the safety database. It may not be a specific number, but would depend on the adverse event pattern.

Looking at other issues, such as the diagnostic clinical criteria, the criteria proposed in the draft guidance will reduce trial feasibility and lead to enrollment of non-representative study populations. And if we look at the left column for the guidance right now, we have a requirement of
greater than or equal to three clinical criteria for diagnosis of HABP/VABP: documented fever, increase/decrease of white blood cell count and such. However, looking at our recommendations, we require greater than or equal to two clinical criteria, with a positive chest x-ray, for the diagnosis of HABP and VABP, because we believe this has the best combination of sensitivity and specificity.

The issue of the CPIS score being required, in this case, the guidance requirement has CPIS as greater than 6 required for eligibility. This is not practical because CPIS is really not validated as a prospective baseline diagnostic tool and remains somewhat controversial, particularly up front in a study. So our recommendations are to not require CPIS as a baseline entry criteria, but, indeed, to collect these data and use them for the assessment of clinical progress.

So, in summary, one trial is enough when another indication is studied. And one trial by itself could be enough for a specific labeled indication, and the labeling would appropriately
include a summary of the studies. And, certainly, the FDA recommendation of a single VABP trial leading to a VABP/HABP indication is a major step in the right direction. And a sponsor may choose to do more, and very often they will. A mortality-plus endpoint makes the most sense. With an odds ratio-based margin, it also helps with the sample size, because, again, it's critical to be able to have reasonable size clinical trials that can be enrolled in a reasonable amount of time.

We still have problems, though, with the issue of prior antibiotics discussed extensively yesterday, and I anticipate to be discussed quite a bit today. If this is not accommodated, we'll be faced with significantly higher clinical trial barriers and continuing studies or initiating studies for antibiotic in HABP and VABP may be very challenging. Also, the less common pathogens, as mentioned earlier, the trial sizes required for an organism-focused antibiotic are staggering.

The setting of breakpoints also is important, and the clinical data must not be the only
factor in determining those. And with regard to entry criteria, the CPIS is an inappropriate means by which to screen patients. Simpler rules are needed.

Thank you.

DR. MOORE: Thank you very much, Dr. Fromtling.

All right. It's 10:15. Why don't we take a 15-minute break? Committee members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience. We will resume here at 10:30 and start with Dr. Laessig.

(Whereupon, a recess was taken.)

DR. MOORE: Okay. We'll get restarted here. Can I have everybody take their seats? We'll need to end the conversations in the back of the room, I'm sorry.

We'll start now with the FDA presentations, with Dr. Laessig.

Thank you, Dr. Laessig.

FDA Presentation - Katie Laessig

DR. LAESSIG: Thank you, Dr. Moore, and good
morning, everyone. I'm having a sense of deja vu, although, in fact, I'm not up here to present the proposed regulatory pathways in trial designs. I'll leave that to my colleague, Dr. Komo, who is better suited to walk you through the complex statistical issues. What I'm here to talk about is a clinical perspective on HABP/VABP trials, sort of past and future, although you'll hear some similar themes to yesterday.

So as I said, I will be talking about some issues with prior trials for these indications, the use of prior antibacterial drugs, the use of concomitant antibacterial drugs, our rationale for the 28-day mortality endpoint, and our rationale for the micro intent to treat as the primary analysis population.

So what were some of the issues we've had with prior trials for this indication and drugs that have not been approved for this indication? Well, some of the drugs in the trials actually outright failed, likely due to inadequate spectrums of activity or inadequate doses for the target bacteria.
In addition, the interpretation of these trials was problematic because there was confounding by significant prior and concomitant antibacterial drug use, which made it very difficult for us to figure out what the treatment effect of the study drug was.

There was also a failure to de-escalate the concomitant antibacterial drugs. There was an inability to determine whether the bacteria isolated from culture were considered to be pathogens requiring adjunctive antibacterial agents. We had issues about questionable interpretations of the chest radiographs. There were inconsistent or absent microbiological specimen collection and assessments; and, finally, a concern that subjects did not actually have the disease of interest, which, as everyone knows, is a big issue NI trials, because it will lead to the erroneous conclusion that the study drug is non-inferior to the comparator.

So here in the next few slides, I'm presenting some of the confounding by the prior antibacterial drug use. The drug names have been de-identified since these were not approved products.
So on this slide, I'm showing drug A, study 1 and study 2. For both studies, the comparator and the study drug have been pooled together. So you can see the first row here. About 20 percent hadn't gotten any prior drugs, prior antibacterials. And then about an additional 20, 25, 26 percent did not get any within the 24 hours prior to study initiation. And then about 50 to 60 percent had gotten something within the 24 hours prior to study initiation.

So this is a single trial for drug B, showing both the drug B arm and the comparator arm. Actually, for this one, they did pretty well. Not that many patients actually had gotten prior antibiotics within the seven-day window; prior to study initiation, two-thirds, about, and then a third had gotten some, and then a small proportion we couldn't tell.

Finally, drug C, again, a single study. So we're back to about two-thirds had gotten priors during the 24-hour window. And then overall in the study, 85 percent of the micro intent-to-treat
subjects had received any prior antibacterials for systemic use. So you can see why this might be an issue for us.

One aside on this, and I apologize. It was sort of an oversight. What I'm not showing is the data about how this impacted treatment outcome. And there wasn't really a consistent pattern, so it's not clear whether this was because the patients who got priors were different, and those analyses may be of sort of questionable value if you think the patients don't have the disease anyway.

So concomitant antibacterial drug use, this is back to drug A, where we're looking specifically at anti-pseudomonal coverage, anti-Gram-negative coverage. So the differences were quite -- or there were differences between these two. So study 1, you had a very large proportion of patients getting concomitant anti-pseudomonal coverage, and, in fact, they were getting it for a pretty long time; so about a third for more than five days. And not surprisingly, a third of the patients did not have pseudomonas isolated, where in study 2, that was a
bit better, and so sort of less than an issue.

Now, this is back to drug C, where you had, again, two-thirds of the patients were getting the concomitants. The mean duration for the three most commonly used was 6.2 to 7.2 days, and the median duration was five to six days; so, again, for a fairly good proportion of the study treatment duration.

Moving on to the problems with the chest x-rays. Some of them were not consistent with pneumonia. Also, there was a lack of formal radiology reports submitted. And then, as Dr. Bennett asked yesterday, insightfully, there were inconsistencies between the radiologists' interpretation and investigator-indicated chest radiograph findings on the CRF. For some of them, we weren't certain who exactly was interpreting the chest x-ray. And then, lastly, for some, there were just no reports at all.

Then there were some problems with micro specimens. The specimens could have been inadequate for culture, and they had a lot of squamous epis, and
they didn't have very many white blood cells. Some of the sputum samples had no Gram stain at all. And then the endotracheal aspirates, again, appeared to be, for some of them, inadequate, with a lot of squamous epis or no bugs. And then there was a lack of standardization for the bacterial quantitation in the bronchoscopically obtained specimens.

Then, lastly, the question of did the subjects really have HABP/VABP at all. So as I've said, there were unconvincing radiologic and microbiologic findings. Some of the patients were enrolled without any findings for pneumonia, such as fever, leukocytosis, or purulent sputum. Some of the subjects appeared to have a less likelihood of disease based on low CPIS scores and/or a low risk of mortality based on low APACHEs.

So now this is moving on to sort of things to bear in mind for future trials. So why are we sort of advocating this 28-day mortality endpoint? Although, again, this is before the committee and we are interested in your perspective on this.

As Dr. Toerner has mentioned, really,
there's no evidence of treatment effect for other endpoints, and we certainly agree clinical response is important, and we want that information, and that should be assessed as a secondary.

With respect to the time point, there are several issues, but one of them is sort of the earlier you look, the lower the rates are going to be. And historically for the control arms, it's been around 20 percent. And as you've heard from previous information, there wasn't a consistent time point at which this was measured either.

Another thing that makes an earlier assessment a little problematic is the duration of therapy. So most of the trials have allowed 7 to 14 days of dosing, although some of them do allow longer, up to 21 days. So in the trials that allowed only 7 to 14 days, there were very few subjects who got more than 15 days. But in the trials that allowed up to 21 days, you had about 11 to 14 percent who did, in fact, get more than 14 days of dosing. So if you move to a 14-day assessment, you'd be, obviously, assessing these patients before they had
finished therapy.

So this is looking at all-cause mortality, again, by different time points, 14 days, 21 days, 28 days, and so these are studies of different agents. And as I've said, you can see how, clearly cumulatively, the numbers go up. But, in fact, you do have some studies that did have higher than 20 percent mortality by day 28, and reasonably close for these other two.

So here it's been broken down by VABP versus HABP, so this is the slide for the VABP numbers. Again, you're getting higher rates if you go out to 28 days. And for VABP -- for three of the trials, you're around 20 percent. This study, obviously, was a bit lower. But as has been pointed out, obviously, these studies were conducted several years ago. There have been changes in management. So whether these types of numbers could still be expected is uncertain.

So why are we interested in the micro ITT as the primary analysis population? Even though we recognize there are limitations, even if you isolate
a bug, maybe it's colonized or maybe it doesn't have anything to do with the infection, it still, in the context of all the other information, helps to increase our confidence that the study subjects have the diseases of interest. And as I've mentioned, there are diagnostic uncertainties. Other speakers have mentioned the same thing. It's a tough diagnosis to make. But when we rely on clinical and radiologic findings alone, I think it increases our uncertainty.

Also, as has been mentioned, fortunately, at least with these two infections, we do have fairly high rates of isolation of bacterial organisms, up to about 70 percent. And in contrast to the numbers presented for Gram-positives earlier, Dr. Komo will present some information from other registrational trials, where even for Gram-positive, you do have a reasonably high rate of isolation of a bug. And then non-culture methods can again be used to supplement conventional culture.

So, in conclusion, although these trials are extremely difficult to conduct, we need to have good
studies so that we can make valid conclusions about the treatment effect of study drugs. So we need strict enrollment criteria to ensure that subjects have the disease of interest. We need well defined procedures for obtaining and evaluating the chest radiographs and, similarly, for obtaining and interpreting microbiologic specimens. We certainly need to minimize as much as possible prior and concomitant antibacterial drugs, and we need to de-escalate once culture results are known.

As I've said, the micro ITT population provides assurance that the subjects have the disease of interest, and around 60 to 70 percent of subjects are usually microbiologically evaluable.

Lastly, mortality is the endpoint for which there is historical evidence of treatment effect. And it looks like 28 days seems reasonable to capture disease-related mortality without too much noise.

So I'd like to acknowledge my colleagues who helped me put this together, and that's all I have.

Thank you.

DR. MOORE: Thank you, Dr. Laessig.
Let's move on to Dr. Komo's presentation.

**FDA Presentation - Scott Komo**

DR. KOMO: Good morning. My name is Scott Komo. I am here to present the proposed development pathways and clinical trial designs for hospital-acquired and ventilator-associated bacterial pneumonia.

This is the outline for my talk. First, I'll present the microbiological evaluability we've seen in some recent trials, and I'll present a brief discussion of our non-inferiority margin justification, and then I'll discuss the risk difference and the odds ratio measures, then talk about the sample size requirements and also the proposed development pathways.

In the next several slides, I will present the microbiological evaluability rates seen in some recent VABP and HABP trials and show how we arrived at the microbiologic evaluability estimates using the sample size calculations that we've seen later in the talk.

This table presents the microbiologic
evaluability rates for VABP patients in trials of broad spectrum agents. You can see that the microbiologic evaluability rates range from 72 to 84 percent.

These are the microbiologic evaluability rates of Gram-positive pathogens for VABP patients in trials of Gram-positive agents. The microbiological evaluability rates range from 56 to 63 percent.

Finally, these are the microbiologic evaluability rates for the HABP patients in trials of broad spectrum agents. The microbiologic evaluability rates range from 50 to 63 percent.

I will now briefly discuss how we determined the non-inferiority margin. More information can be found in the appendix of the backgrounder, as well as the Sorbello 2010 Drug Information Journal paper.

A fixed margin approach was used to justify the non-inferiority margin. To determine the
historical evidence of treatment effect for this active comparator, a literature search identified 36 published studies. Unfortunately, no placebo-controlled studies were identified, so we were not able to directly estimate the treatment effect. Also, no placebo data for assessing clinical response was identified.

Thus, to estimate the effect of placebo, we used the studies of patients who received inappropriate, inadequate, and delayed therapy and looked at all-cause mortality. For the active comparator, we used recent randomized clinical trials of effective therapy.

To estimate the placebo mortality rate, we identified 12 studies of patients receiving inadequate, inappropriate, or delayed therapy. Using the two studies thought to be the most comparable to the active comparator trials with respect to the baseline agent APACHE-II scores, the all-cause mortality estimate was 62 percent, with a 95 percent CI of 52 to 71 percent. It should be noted that if you used all 12 studies, a similar estimate was found.
with an all-cause mortality estimate of 60 percent, with a 95 percent CI of 49 to 69 percent.

To estimate the active control mortality rate, eight randomized clinical trials were identified. Five trials were used in the analyses because they were felt to be the most comparable to the placebo trial studies. The all-cause mortality estimate for the five trials was 20 percent, with a 95 percent CI of 18 to 23 percent.

This slide shows how we derived the observed treatment effect for the active control. Using the 95 percent confidence bounds for the placebo and the active control all-cause mortality estimates, we took the difference between the lower bound of the placebo estimate, which was 52 percent, and the upper bound of the active control estimate, which was 23 percent. This resulted in a cross-study difference of 29 percent.

I will now discuss the limitations of the approach used. First, there are no placebo-controlled studies, so the historical treatment effect could not be directly estimated. Also, the
observed treatment effect for HABP and VABP was derived from seven studies, two placebo and five active control. Also, across studies, there was variability in the baseline patient demographics and disease severity reported. In addition, the patients in the placebo studies were not always that well characterized.

Also, the studies assessed mortality at different time points or did not state specifically when the mortality was assessed. Also, the cross-study comparisons create uncertainty due to the concern of the comparability of the patients. And, finally, the changes over time in ICU patient management lead to the potential concerns of the constancy of the treatment effect.

I will now discuss the concept of discounting as it relates to the determination of M1 or the statistical margin. Discounting is performed to account for uncertainties in the active comparator treatment effect. Accounting for the variability by taking the difference in the upper bound of the active comparator rate and the lower bound of the
placebo rate can be viewed as a form of discounting, but may not account for all the potential biases that were listed in the previous slide. That is why further discounting was taken that resulted in an M1 of 20 percent.

The choice of M2 or the clinical margin is based on a clinical judgment as a proportion of M1 that can be lost, but the drug still considered non-inferior. A large proportion of M1 was preserved because the endpoint is all-cause mortality. Thus, we arrived at a 10 percent non-inferiority margin based on a 50 percent preservation of M1.

It should be noted that there have been some comments that the amount of discounting used was too large. However, it should also be noted that if one discounts less and, at the same time, was unwilling to accept more than a certain magnitude of absolute mortality increase, such as 10 percent, then a larger proportion of M1 would then need to be preserved. So you'd arrive still at the same spot.

I will now discuss three potential measures that could be used to estimate the treatment effect.
in our proposed trials. I'll first discuss the risk
difference, which is the difference in probabilities.
This would be the measure of the absolute difference
in mortality risk. This is the measure that has been
traditionally used in these trials. The next measure
is the relative risk, which is the ratio
probabilities. This is the measure of the relative
increase in mortality risk. Finally, the last
measure we'll discuss is the odds ratio, which is the
ratio of the odds of event occurring in the test
group to the odds of it occurring in the control
group.

Here are the hypothetical results of a trial
with 1,000 test patients and 1,000 control patients.
To compute the risk difference, we take the
difference of the mortality risk, 25 percent in the
test group and 20 percent in the control group, and
this gives a risk difference estimate of 5 percent.

Using the same hypothetical data that was
used for the risk difference, we compute the relative
risk as the rate of 25 percent mortality rate in the
test group and 20 percent mortality risk in the
control group, giving a relative risk estimate of 1.25.

To interpret the relative risk, a relative risk of greater than 1 shows an increased risk of mortality for the test drug, while a relative risk of less than 1 shows a decreased risk of mortality for the test drug. And a relative risk of 1 shows similar risks for the test and control trials.

Using the same hypothetical data as was used previously, we can calculate the odds in each treatment group as the probability of dying divided by the probability of surviving. So, for example, in the test group, the odds is 0.25 divided by 0.75. Then we can compute the odds ratio as the ratio of the odds in the test group divided by the ratio of the odds in the control group. The resultant odds ratio here is 1.33.

I will now discuss the interpretation of the odds ratio. So an odds ratio of greater than 1 shows an increased odds of mortality in the test group compared to the control, while the odds ratio of 1 shows no difference in odds of mortality in the test group.
group compared to the control. And finally, an odds ratio of less than 1 shows a reduced odds of mortality in the test group compared to the control.

I will now discuss the concept of symmetry. By symmetry, I mean whether the analyses give similar results regardless of whether you look at mortality or survival or, alternatively, success or failure.

So, first, let's look at the odds ratio measure. For mortality, the odds ratio is 1.33, while for survival, the odds ratio is 0.75. You can see that the odds ratio for survival is the reciprocal of the odds ratio for mortality. Thus, the odds ratio is symmetric.

If you look at the relative risk, the relative risk for mortality is 1.25 and the relative risk for survival is 0.94, but the reciprocal of the relative risk for survival does not equal the relative risk for mortality. Thus, the relative risk lacks symmetry.

While the relative risk may be easier to interpret, the odds ratio has good mathematical properties, and the odds ratio is symmetric to the
mortality or survival, while the relative risk is not symmetric, which is the major disadvantage. The odds ratio approximates a relative risk when the control rate, event rate is low.

As has been mentioned today, there is a concern that the mortality rate is likely less than 20 percent. We have also received comments suggesting that the mortality rate would likely be markedly lower than historical mortality rate estimates of 20 percent. Some estimates were in the 10 to 15 percent range.

If this is true, then the first thing -- there is a concern as to whether the historical treatment effect would still hold in this case with a markedly lower control mortality rate. This is critical as it underpins the non-inferiority margin justification.

Note, this is an issue for all of the measures we previously discussed. If it is reasonable to assume that the historical treatment effect would still hold in this case, there are still concerns as to the choice of the right metric.
If the control rates are lower than historical rates, the risk difference may not be the most appropriate measure and the odds ratio may be better. If the control rates are higher than historical data, then the odds ratio may have additional benefits with regard to sample size.

In the next two slides, I'll compare the risk difference of the odds ratio to illustrate these points.

This graph shows the relative increase in mortality for the risk difference and the odds ratio measures using a non-inferiority margin of 10 percent for the risk difference and a non-inferiority margin of 1.71 for the odds ratio. On the odds ratio scale, an NI margin of 1.71 corresponds to a 10 percent absolute increase in mortality if the control rate was 20 percent, which was the rate seen in the historical active control studies.

The appropriateness of the non-inferiority margin is affected by the control mortality rate. For example, if the control mortality rate was 1 percent, an NI margin of 10 percent is likely not
acceptable, as this would translate to up to an 11-fold increase in mortality.

From this graph, it can be seen that the relative increase in mortality changes much more slowly for the odds ratio than for the risk difference. Specifically, there are questions on the appropriateness of the 10 percent NI margin for the risk difference if the control mortality rate is markedly lower than 20 percent. If the control mortality rate was 20 percent, the relative increase in mortality is the same for both measures, with an up to 50 percent relative increase. However, if the control mortality rate is 15 percent, the relative increase in mortality is 67 percent on the risk difference metric and 55 percent on the odds ratio metric. If the control mortality rate falls to 10 percent, then there could be up to a twofold increase in mortality on the risk difference metric and a 60 percent relative increase in mortality on the odds ratio metric.

This graph shows the sample size requirements for the odds ratio with a 1.71 non-
inferiority margin and the risk difference with a
10 percent non-inferiority margin. These are the
sample sizes for 80 percent power, assuming a similar
mortality rate for the test drug and the control.

Notice as the control mortality rate
increases, the required sample size when using the
risk difference increases. Because we would like to
increase specificity by enrolling sicker patients to
better discriminate between effective and less
effective treatments, this would cause an increase in
the required sample size. This phenomena does not
occur for the odds ratio measure, where the required
sample size decreases as the control mortality rate
increases. So using the odds ratio might make it
feasible to conduct trials enrolling severely
affected patients.

I'll now present the proposed development
pathways. The first option is a single VABP trial
plus supportive evidence in a related indication.
This would provide evidence for both a VABP and HABP
indication. The total number of randomized patients
for the risk difference is 720 patients, providing
80 percent power, or 962 patients, providing 90 percent power. On the odds ratio scale, 952 patients would provide 80 percent power and 1272 patients would provide 90 percent power. This assumes a 20 percent control mortality rate and a 70 percent microbiologic evaluability rate.

The next option is a single HABP trial plus supportive evidence in a related indication. This provides evidence for a HABP indication. The total number of randomized patients required are as follows. For the risk difference, it's 840 patients, assuming 80 percent power, and 1124 patients with 90 percent power. On the odds ratio metric, it's 1110 patients with 80 percent or 1484 patients providing 90 percent power. Again, this assumes a 20 percent control mortality rate and a 60 percent microbiologic evaluability.

I'll now discuss the supportive evidence. This would be adequate evidence of efficacy and safety in a related indication, such as complicated intra-abdominal infections. This would be for drugs primarily active against Gram-negative bacteria.
Alternatively, another would be CABP, community-acquired bacterial pneumonia. This would be for drugs with a suitable spectrum of activity for the treatment of CABP.

Finally, it would be acute bacterial skin and skin structure infections, and this would be for drugs with activity against only Gram-positive organisms, including methicillin-resistant staphylococcus aureus.

The third option would be two VABP trials. This would provide evidence for both HABP and VABP indications, and the total of randomized patients for the program required are -- for the risk difference, it's 1440 patients, with both trials powered to 80 percent, or 1924 patients, with both trials powered at 90 percent.

On the odds ratio scale, it's 1904 patients with both trials powered at 80 percent and 2,544 patients with both trials powered at 90 percent. All these estimates assume a 20 percent control mortality rate and a 70 percent microbiologic evaluability rate for both trials.
The last option is one HABP and one VABP trial. This would provide evidence for both a HABP and VABP indication. The total number of randomized patients for the program are as follows. On the risk difference scale, it's 1560 patients with both trials powered at 80 percent or 2,086 patients with both trials powered at 90 percent. On the odds ratio scale, it's 2,062 patients with both trials powered at 80 percent or 2,756 patients with both trials powered at percent. Again, all these calculations assume a 20 percent control mortality rate and a 70 percent microbiologic evaluability rate for the VABP trial and a 60 percent microbiologic evaluability rate for the HABP trial.

So, in summary, the proposed development pathways we discussed are a single trial with supportive evidence or two trials. The proposed primary endpoint is 28-day all-cause mortality and the proposed primary analysis population is the microbiological intent to treat. We've discussed the risk difference and the odds ratio measures and, also, proposed margins are 10 percent for the risk
difference scale and 1.71 for the odds ratio scale.

Thank you. And I'd like to acknowledge my colleagues who helped me in the preparation of this presentation.

Clarifying Questions to the Presenters

DR. MOORE: Thank you, Dr. Komo. And thanks to the FDA presenters. Obviously, a tremendous amount of work went into this, and we appreciate it.

We're going to move now to the clarifying questions to the presenters. Dr. D'Agostino?

DR. D'AGOSTINO: I'd like to address this question to Dr. Komo. I followed your discussion of the risk difference and the odds ratio, and I do want to say, to preface this, I have been in the situation where we had a historical control rate of 50 percent and we designed a risk difference, and the margin was going to be 10 percent. And then it turned out that our observed rate was 30 percent as opposed to 50 percent. We did wonderful things, but the difference of 10 percent threw us all in a spin, and the change from constancy -- it wasn't constant rates in the control. And I think that's going to be given
that non-inferiority -- when we give the spiel about
non-inferiority, we say there should be constancy and
consistency, but there isn't, in reality. So this
changing rate, I think, is very important. And I
think the odds ratio, as you presented, is a sort of
reasonable way to do it.

You put down the relative risk because you
said it's not symmetric. But in designing these
studies, in designing non-inferiority trials, which I
do quite a bit, what we'd like to say is -- using
mortality as the outcome, we'd like to say, well, we
want to be within the 50 percent increase of
mortality. And we're never trying to play the game
of shifting to survival, but mortality is the
endpoint. And if you say that the margin is 1.5,
which it would be in this case here, if you said
you're going to have a 50 percent, then the changing
p-value, or the changing control rate is not
necessarily a problem. You have to have taken it
into account in sample size, but it's not necessarily
a problem. And the relative risk has such an appeal
to it, you know when you see 1.5, you're talking
about -- you're willing to tolerate a 50 percent increase or less than a 50 percent increase.

The odds ratios, everybody's scratching their heads in terms of what it means.

Why did you discount or not pursue the relative risk? I don't buy the argument of the symmetry, because you can say you must focus on mortality for the endpoint.

Is my question clear?

DR. KOMO: Yes. Thank you. It's twofold. I think -- we actually were a little concerned with some of the symmetry because in some ways, we were kind of concerned that you can, depending upon how you frame it, whether you look at survival or mortality, you like to get similar results.

The one other thing I should note is the sample sizes required for the relative risk are even higher than those for the odds ratios.

DR. D'AGOSTINO: I'm aware of that, too.

DR. KOMO: We were having discussions about the feasibility, too. So that was also one of the issues.
DR. D'AGOSTINO: Once you shift from the
difference -- that's where I was wondering, was the
sample size thing, the relative risk. Again, it's
crystal clear when you look at it. And I think for
the people who aren't statisticians at the table, if
you have a relative risk of 1.5, it's saying that
you're willing to tolerate an increase in mortality
up to 50 percent from the control group. If you have
an odds ratio of 1.71, what does it mean? And you
have to sort of re-translate it and so forth.

So the relative risk has a purity I think in
terms of face, but it does have a consequence in
terms of sample size. And in the things I'm doing,
we're willing to live with that, because the FDA that
we're dealing with wants the relative risk. They
want to have a sense of that.

So I think that it's not necessarily a
resolved issue in terms of odds ratio. I think we
have to move away from risk difference because of the
changing, but relative risk versus odds ratio, I
think that you might want to say that the companies
can sort of play that out the way they please to do
as opposed to stick to an odds ratio.

   DR. KOMO:  Agreed.

   DR. MOORE:  Dr. Masur?

   DR. MASUR:  I have a question that I guess
could be addressed to Tom File or Don Craven or to
Katie Laessig.

   One of the things I guess I'm uncertain
about in how to analyze these trials is how to
approach drugs which often have very different
purposes for ventilator-associated pneumonia. We
have some drugs that are sort of backbone drugs, like
an imipenem or a Peptazol. We have some that are
very specific, say, for MRSA, we're looking at vanco
versus linezolid. We have others that are specific,
say, for Gram-negative, we're looking for something
to substitute for colistin, for acinetobacter.

   So when you start an empiric regimen, you're
going to often use multiple different drugs, and,
presumably, you put an investigational drug up
against something else. How do you wind up then
interpreting the study when you are, let's say,
looking at vancomycin versus linezolid, and the only
thing you get out of your culture is acinetobacter?
These become very complex, and often the
microbiologic data shows you that the drugs that
you're looking at are irrelevant or potentially
irrelevant to the outcome.

So how do you wind up interpreting the data
when these drugs have a variety of different
functions, and they may not match up with the
organisms that you recover?

DR. LAESSIG: Well, when they don't match
up, we tend to not include those organisms in our
microbiologically evaluable population. So if it
were a drug for Gram-positives, as you say, and
isolate a Gram-negative, then we wouldn't include
those.

Is that what you're asking?

DR. MASUR: Well, I guess that means you
then you wind up with very high Ns that you need when
you say they're microbiologically evaluated, and you
also get into the issue that you get predominantly
MRSA. Your Gram stain shows MRSA, but then you
culture a small amount of acinetobacter.
Do you then decide that that is colistin relevant? How do you interpret those data? To me, it becomes very confusing to know whether or not your drug is plausibly going to have an effect.

DR. LAESSIG: I guess I would say that if there are -- for a Gram-positive drug, and you have a Gram-positive anagram-negative, we probably would still include those in the evaluable population. We tend to cut the data and look at it all manner of different ways to try to see what's going on with it.

So I don't know if any of the statisticians want to jump in with any response about that, but that's sort of what we generally tend to do. But I agree it oftentimes ends up being sort of case-by-case.

DR. MOORE: Go ahead. Dr. Cox, and then Dr. Craven.

DR. COX: I'll come back.

DR. MOORE: Okay. Dr. Craven.

DR. CRAVEN: I think it's a really great question, and I think one way to circumvent this, particularly if you're looking at ventilator-
associated pneumonia, is that there's been a lot of studies out looking at surveillance cultures. And, generally speaking, the surveillance cultures that you do on day 2 and day 4 are pretty much the same organisms you see on day 4 and day 5.

So if your surveillance culture has MRSA and pseudomonas or MRSA and pseudomonas only, at least you know, if you're looking at antibiotic A versus antibiotic B, that that patient would be a good candidate for treatment.

Now, there's going to be exceptions to the rule, but at least in the prospective studies we've done where we've done daily cultures every day, some people do them every second day or third day, if these people are going in clinical trials, you can at least know that the person that develops clinical signs has microbiologic criteria, has an enter point to go into that study that would compare antibiotic A to antibiotic B.

I think a lot of labs now can just use a regular tracheal aspirate that can give you a pretty good indication that when you enter a person in the
trial, that they're going to have bacteria that would
be susceptible to the antibiotic that's being tested
against a traditional antibiotic, and you don't have
to use broad spectrum antibiotics and try to
de-escalate by the time you get into the trial.

So that would just be a study design that I
think would be reasonable to try to maximize efficacy
about enrolling people that can be tested without
trying to enroll people and then trying to throw
people out that don't have the organism that's being
examined in the trial.

DR. MASUR: Just to perseverate for one more
minute. Then let's say, Don, for instance, you were
looking at imipenem versus a new penem and the
patient had been colonized with MRSA. You decide
then to use vanco plus meropenem or vanco plus your
new penem, and all you got from your culture was
MRSA. Now many people would feel that the pneumonia
is likely to be polymicrobial anyway.

So do you throw that out from the penem
comparison and consider that vanco is your only
active drug, or do you say we're going to leave it in
because it's probably multivector? And I'm not being
critical of the fact that it's hard to have an
answer. I'm just wondering how you analyze the
trials and then whether you need to put 3,000
patients in to get 700 evaluable.

DR. CRAVEN: I think your point is a good
point. Obviously, I wouldn't look at
antibiotic -- two carbapenems to see what efficacy it
would have against staph aureus, because that would
really not be what you're going to. So you'd be
looking at vancomycin versus linezolid for that
trial. That's what I'm saying, that --

DR. MASUR: Well, that's assuming that
there's only one -- that when you get MRSA, that's
the only pathogen, which maybe you'd assume or maybe
you wouldn't.

DR. CRAVEN: Well, I'm saying I think that,
generally speaking, that what people are initially
colonized with that stay ventilated over a period of
time, most of the time, that bacteria is the same
bacteria that's there three days later when they
develop signs and symptoms of pneumonitis.
So there is polymicrobial pneumonia, and some of these patients have more than one organism on day 3 and day 4. But if they don't have a Gram-negative rod and you're doing a trial against carbapenems, and it's staph aureus, I don't think that's going to be very helpful to see what effect a carbapenem would have.

But I think there are study designs that can maximize your enrollment and be able to identify people that are actually going to be able to look at antibiotic A versus antibiotic B for a Gram-negative rod. So you'd be looking at pseudomonas, e. coli, klebsiella, and all the other organisms, if there. But if it was only staph, I don't know how you could really conclude anything about a carbapenem efficacy if you're using vancomycin and a carbapenem.

DR. MOORE: Dr. Cox?

DR. COX: So consistent with the comments that have been made -- and it's a great question, Henry, and I think it brings to bear one of the considerable challenges of doing HAP/VAP studies.

Since most of these trials -- many of these
trials will -- most, all will be non-inferiority trials, if you're going to assess the test agent, you really have to move to the population of patients in whom the test agent can have its effect. So if it's a Gram-positive-only agent, those patients who have Gram-negative pathogens, presumably it's the adjunctive concomitant therapy that's having its effect there. So it's not really a means to assess the effect of the Gram-positive active -- only Gram-positive active agent.

So, yes, we do look at the microbiologic information to help guide us to the population, that it's informative to look at the effect of the test drug. And that does have implications for sample size and can make doing the trials challenging, maybe even a little enriched, to some degree. But still, it can be -- for more limited spectrum agents -- and we heard this, too, in the PhRMA presentation -- it also brings to bear additional challenges in order to be able to enroll the patients with a particular pathogen or group of pathogens of interest where the agent has its effect.
So it's a good question. It has implications for what the appropriate analysis population is in order to be able to informatively assess the drug and, also, implications for sample size and, also, I guess this issue of some of the practical issues of these trials that are really challenging.

DR. MOORE: Dr. File?

DR. FILE: I'd like to respond to what Henry asked about the question, because it is very appropriate; we see this all the time. But from a clinical perspective, I've always considered endotracheal aspirates fairly sensitive, maybe not specific, but fairly sensitive. And from an antibiotic stewardship, which we've been doing very extensively now, if I had that type of patient and it's a good specimen, and we're just isolating MRSA, I'm confident about stopping the Gram-negative because of that.

But one other strategy I might add to what Don said about using surveillance cultures, frequent surveillance cultures -- and I sort of hesitate to
say this in light of what Melvin said yesterday about
molecular studies, but there are molecular studies
now that can identify right away pseudomonas,
acinetobacter, and, certainly, we've all been using
the MRSA molecular studies. And so that can be done
right away to help identify the potential pathogens
for that problem.

DR. MOORE: All right. Thanks. Let's get
to Dr. Neely.

DR. NEELY: I wanted to go back to
Dr. D'Agostino's question. I struggled with the
subtleties of the discussion between risk difference,
relative risk, and odds ratio. But it's important
because it obviously impacts sample size.

Could you clarify, Dr. Komo, or even
Dr. D'Agostino, why was it such a major disadvantage
that the relative risk was asymmetric, if you can, in
non-statistical terms for us clinicians?

DR. KOMO: Well, if you did an analysis for
survival and you did an analysis for mortality, you
could get different results, whereas on the odds
ratio, you would get the same results, similar
results.

DR. NEELLY: But our endpoint -- if the trial's endpoint was mortality, why is it such a horrible thing if we weren't --

DR. D'AGOSTINO: That's the point I was trying to raise, asking. We say mortality is the endpoint -- don't flip to survival; mortality would be consistent -- then it's a simpler thing to look at. But there are sample size implications that come into this here. But it's just a simpler thing to interpret I think with the relative risk, and I'm not so sure it should be taken off the table.

DR. MOORE: Dr. Wiedermann?

DR. WIEDERMANN: Yes. I have three questions, but I'll only do one, and hope if the other two don't get covered, I may try to come back. But since we're on the statistical question, I had another question for Dr. Komo.

I'm wondering what -- if the true mortality rates are 15 percent or 10 percent rather than 20 percent, what does that do to sample size requirements in your -- well, you can choose the odds
ratio.

    DR. KOMO: If you can give me a minute, I
can pull that up. So I can get back to you.

    DR. MOORE: Dr. D'Agostino?

    DR. D'AGOSTINO: I think this is a very
important question in terms of sample size, but I
think it's also a question in terms of when you get
the results. Say you're going in with the
anticipation of a 20 percent mortality rate in the
control, and it turns out the control is only
10 percent mortality rate and say the treatment is
20 percent. That's a twofold increase.

    Would you say, hey, there's something wrong
with the way we designed the study and so forth that
I'm not going to allow you to have a risk difference
of 10 percent when it corresponds to a whole hundred
percent increase in event rates?

    I think those are things that aren't
necessarily laid out in what we have. And the FDA
is, obviously, aware of them, but I think those are
implications in terms of how one has to proceed. And
I'd like to just add to the question; how would the
FDA respond to that?

Thank you for allowing me -

DR. MOORE: Sure.

Dr. Komo, did you have something you wanted to bring in?

DR. KOMO: Sure. Let's see. Odds ratio for 15 percent, with 80 percent power, it's 416 patients. I need to get back to you on this one.

DR. MOORE: Dean, did you have a question?

DR. FOLLmann: Yes. I had a question. I also guessed I should comment on this issue, as well. I thought about this a bit before the meeting, about the odds ratio and the risk difference and all that, and I find odds ratios a little harder to interpret, as well.

One thing that caught my eye and I thought someone would bring up, actually, is look at the difference in the sample size for the risk difference of 10 percent and the odds ratio of 1.71. The odds ratio of 1.71 is bigger, maybe 500 people bigger for the two trials.

Now, how could that be? If we're sort of
trying to derive the odds ratio based on a risk difference, I would have thought the sample size would be different.

I understand how this happened, and, basically, the FDA said let's assume a control event rate of 80 percent survival and a treatment event rate of 70 percent, and that leads to the odds ratio of 1.71 and a risk difference of 10.

There's another way to do it, which might seem a little more backwards or something, but you could say let's suppose a pooled treatment and control event rate is .8. That leads to a control event rate of .85, a treatment event rate of .75, and an odds ratio of 1.89. If you use that odds ratio, you have the same sample size. So, in some sense, that equilibrates -- if that's a word -- the risk difference of 10 percent to the odds ratio. It's sort of a very similar trial that would have the same performance if the control event rate is .8.

So in some ways, that's maybe a technical comment. Maybe it's an argument that maybe 1.89 could be considered for the odds ratio. I don't want
to say anything like super-strong about that, but I think precisely how you do it has big implications in sample size. We know that little changes in the parameters have a profound impact. The risk difference of 1.5 was mentioned, and that's just another kind of convenient number. It doesn't equilibrate really to the 20 percent death rate, 10 percent risk difference that we sort of settled on yesterday.

I kind of like that. Maybe that'll be a convention, in a way, like .05 is a convention, and we don't have to revisit, oh, should we use .06 instead of .05 for significance and so on.

So, anyway, this is a little rambling, but I've thought about this and struggled with it, and that's my comment on it, I guess.

I did have a question, as well, unless -- it should be yes/no. It's quite different, though.

DR. MOORE: Go ahead.

DR. FOLLMANN: Go ahead?.

DR. MOORE: You are next in line for questioning.
DR. FOLLMANN: Okay. This has to do with prior antibiotics. So yesterday we had the fortune or misfortune, I guess, of having data that actually addressed the issue, and it seemed to persuade many of us that prior antibiotics was a problem in CAP.

Today it's a little different, different disease and so on, and also the data, from what Dr. Laessig said, to me, there is some data, and the data does not suggest a masking effect of prior antibiotics.

Now, we haven't really seen that. I guess it's not completely analyzed or something. But that's important information, I guess, to think about this issue. Data is very helpful for something like this, obviously. But based on what Dr. Laessig said, I'm concluding, basically, there's some data that addresses this, but it doesn't really show a smoking gun. It doesn't really show a masking of the prior antibiotics on an effect.

So I don't know if you want to say that's a fair assumption for me to make, or am I over-interpreting what you said?
DR. LAESSIG: Yes, I was trying to sort of caveat it pretty heavily that there was not a consistent pattern that we saw, and this is based on just from what Dr. Komo and I can recall. So we would have to look back to confirm it. But, yes, my sense is that there wasn't a consistent pattern, but then that was with the caveats of we don't remember whether there were differences between those two groups of patients that would account for those findings. And, again, those were data from some trials that we were unable to draw conclusions about treatment effect overall anyway, so then that kind of limits the utility of those other analyses.

DR. FOLLMANN: Right. You can't sort of identify masking unless you have like a difference between the two groups to begin with. And so it's not a lot of data, I guess, really to inform that.

But in the questions 4-A and 4-B, there's a distinction appropriately made between patients who first get antibiotics and then develop a disease, so like drug and then bug, and then the opposite, where they have HAP or something, they get empiric
antibiotics, and then they're randomized. This seems very different.

I was wondering if you had information on the rates of that. You mentioned the studies where prior antibiotics ranged from maybe 20 percent to 60 percent, and it would be comforting, I guess, if a lot of that was people who developed the HAP/VAP when they had prior antibiotics or something else. And so this HAP developed in the presence of antibiotics, in which case you would, I guess, think that it's fair to try and test it and try and test the trial that's comparing the new antibiotic.

So, anyway, did you look at the difference in prior antibiotics by first drug and then bug or the other way around?

DR. LAESSIG: I don't remember that we did those analyses. If there were failed trials that came in, they just come in as complete study reports. We don't really do intensive analyses on those. For the ones that did come in, actually, as NDAs, I don't remember -- and I don't know, Scott, if you do either -- whether we did that type of analysis. But
I'm not remembering it.

DR. FOLLMANN: Maybe people on the committee might have a guess about that question. How common is it to get a HAP/VAP when you're on antibiotics for something else to start with?

DR. MOORE: Anybody want to weigh in on that? Dr. Weinstein?

DR. WEINSTEIN: I think we see it all the time. When I'm on the -- in fact, I was going to ask Dr. Craven and Dr. File to comment on that.

People are on antibiotics, and then they develop -- they're in the ICU, they're on event, they develop new fever. Maybe, hopefully, if we're going to really try to diagnose a ventilator-associated pneumonia, they're going to develop a new infiltrate.

Then the question is do you ignore the antibiotics that they've been on because what they've probably gotten infected with is an organism which is not susceptible to the antibiotics that they're on, in which case, why invalidate those patients as potential subjects for a study because they've, quote, "been on antibiotics."
So the question is do you agree or disagree.

DR. FILE: Oh, I agree. Just like it was mentioned, if they've already been on antibiotics -- like the example I showed, this patient who was on actually a second generation cephalosporin for intra-abdominal sepsis, but is on the ventilator, and now develops a secondary pneumonia -- by the way, that happened to pseudomonas, by the way. But at any rate, so I think those would certainly be valid, and, actually, studies show that those patients have a higher mortality than if they weren't on antibiotics for something else.

I think the other issue, however, that was also asked, which is really important to know, is what percentage of the patients received an antimicrobial agent at the time they developed their HAP/VAP and then it was given just before enrollment, because from a logistical standpoint, that's what we see. And that's why it's very difficult for us if we tried to use -- tried to enroll patients before that.

That's mainly -- because when I talk to our
intensivists, they're aware of this data, this sepsis data. You delay one hour, you increase the -- or per hour, you increase the mortality rate 7 percent per hour. They're quite aware of that. So to not allow them to do that when we realize, again, as I said yesterday, it takes us two-plus hours to get consent, much more difficult in ICU than in the general ward or in the ED -- and with all the logistical issues related to that, they won't accept not giving an antibiotic as expeditiously as possible. They will accept just giving one dose of what they consider to be an appropriate antimicrobial agent and then trying to get consent.

DR. MOORE: Dr. Laessig, did you have a comment?

DR. LAESSIG: Yes, I did. I think that we wouldn't necessarily have a problem with that. It all has to do with how that information is captured and reported on the case report form, so that we have a clear understanding that that's, in fact, what happened.

DR. MOORE: I think that's the key element.
Dr. Valappil, where are you? There you are.

Yes.

DR. VALAPPIL: I just want to follow-up on what Dr. Follmann has asked. This is regarding the odds ratio, the risk difference, what you see at the 20 percent control rate. Just in the marginal 1.71 to 1.89, if you enroll severe patients, that is at 25 percent control rate, then odds ratio, risk difference would have essentially similar sample size. And as the severity of the patients increases, 25-plus, then the risk difference would require a smaller sample size than the -- I'm sorry -- then the odds ratio would only require a smaller sample size than what would be required for the risk difference.

The difference, what you see at the 20 percent is because the test statistics are different, and also the variance that is computed based on other methods is also different.

DR. FOLLmann: Right. I'm just saying there are different ways to equilibrate it. You chose one and there are some consequences. There's another way to do it. It corresponds to a larger odds ratio,
which means a smaller sample size and maybe less
evident. So just some discussion I wanted to bring
out, because I struggled with it before.

DR. VALAPPIL: So thank you.

DR. MOORE: Dr. Goetz?

DR. GOETZ: I have two questions. The first
is although it's not as much of an issue of a true
ventilator-associated pneumonia, with many of the
hospital-associated bacterial pneumonias, there's a
question of how we can distinguish between an
aspiration pneumonitis event, which is self-limited,
and true pneumonia. And I wonder if Drs. File and
Craven can address how that's been done in clinical
studies or whether the FDA has an opinion about that.
This is a very troubling issue for us in our medical
wards, and we certainly find that -- and my concern
is that it will bias us toward a no event, because
pneumonitis, per se, does not benefit from
antimicrobial therapy.

Then my second question regarding clinical
trials conduct is it's distressing to see the
duration of polymicrobial and antimicrobial therapy.
Now, certainly, many people need it because they have more than one infection and more than one pathogen. But I'm wondering what practical challenges have been faced in de-escalation and whether that's been a strict part of study protocols that physicians have found it impossible to comply with.

DR. MOORE: Thank you.

Anyone care to answer that? Dr. File?

DR. FILE: Let me just respond. First of all, with aspiration, Don very elegantly talked about that we all aspirate every day. So, virtually, all the pneumonias are aspiration pneumonias. But I suspect what you're discussing is trying to differentiate Mendelson syndrome or aspiration of assayed gastric -- okay.

Of course, that would be based on the epidemiology, if you see that, because we know that antibiotics don't benefit that type of patient. But if you've got a patient who's intubated, and you can do endotracheal aspirates, and you can do the Gram stain right away, although you may have to -- like John said yesterday, you may have to go a half mile
to the lab, whereas we didn't have to do that 15 years ago, but now we do. But, nevertheless, we can look and see if, indeed, there are pathogens there that would reflect a true bacterial pneumonia.

Now, what was your second question? I forgot already.

DR. GOETZ: My second question addressed efforts that have been made in clinical studies to promote de-escalation, and where are the impediments to getting physicians participating in studies to abide by that.

DR. FILE: That's a good point. And in Dr. Toerner's presentation, he appropriately said that based on the workshop that at the time -- remember, that was two and a half years ago -- that was not a common practice. That was true de-escalation.

I can remember even in our setting, in our ICU, trying to convince our intensivists that at day 3, if they have an appropriate culture and we can de-escalate, we should do that. I mean, if the patient was doing better, they would prefer to
maintain the regimen because of that, because of the clinical response.

But then once you start -- that's why I showed this data, this review article from Mike Niederman that showed multiple studies now that -- and if you combine them all, there's definitely a trend that true de-escalation -- but I also call it optimization because it's more than just de-escalation. It's making sure that you have the right dose and the right antibiotic, et cetera.

In addition to stopping the adjunctive therapy, there's general need. If you've got them on MRSA and there's no MRSA, stop it. If there's no pseudomonas, you can de-escalate down from Peptazol to even cefazolin, because e. coli is pan-susceptible or klebsiella, then we should do that.

But now we've been able to convince them because of the publication of those studies, that it's important for best patient outcomes that we do that. The argument that we're going to reduce resistance and all this wasn't as important as the argument that it really has an impact on that
patient's outcome. So when we can say that if we just de-escalate this patient, this patient is going to do better, the mortality is less, and three studies showed that, then we were able to convince them to do that.

I would also say now that just in the last two years since the workshop, whereas maybe de-escalation as part of antibiotic stewardship was not a common process, now it is. The hospitals that have comprehensive antibiotic stewardship programs, of which one of the principles is de-escalation, is increasing logarithmically. And those of you who are from California know that you have to do this. It's legislated. And I think CMS and the Joint Commission is going to require that we all have antibiotic stewardship programs.

We've been doing a comprehensive for a year, and that's one of the main things we do is that ICU day 3, day 2, we get a culture, we're de-escalating. And now our intensivists who two years ago were very hesitant to agree to that now are our most vigorous proponents to do that, because they really feel that
it is providing the best care to the patient.

    DR. MOORE: Thank you.

    Dr. Bennett?

    DR. BENNETT: I'd like to ask Dr. Craven about the formation of biofilms on endotracheal tubes. It's my understanding that we don't change endotracheal tubes very often, and with time, they'll get their own biofilm, certain organisms having more of a propensity to form a biofilm than others. And this has an impact, I thought, upon the results of your endotracheal aspirates that you're using in the patient who shows up with ventilator-associated pneumonia, so that earlier in the course of ventilation, you might trust the results more than later on.

    So what's the facts?

    DR. CRAVEN: I don't know if I have all the facts, but I'd say biofilms are extremely common, and the longer the person is intubated, virtually all patients have biofilms by three or four or five days. The biofilms are generally generated by the bacteria that are in the endotracheal tube and in the lower
airway.

So an example, if it's pseudomonas or whatever, those are basically the same bacteria that are in those biofilms. And biofilms are extremely dangerous, and they're hard to evaluate in clinical antibiotic trials because a lot of antibiotics don't penetrate biofilms very well.

So that's kind of the elephant in the box. But there are new tubes out now that definitely decrease biofilm, like the Bard study, the silver-coated endotracheal definitely reduces biofilm formation. But these biofilms, the longer you're intubated -- we don't change endotracheal tubes. Sometimes at 10 and 14 days when you're take an endotracheal tube out, and you look at the diameter of that tube, the diameter is maybe only 50 percent or 60 percent of what it was. And that's because you have this gelatinous biofilm, which is very difficult because the bacteria are very difficult to eradicate from the biofilm.

So biofilms are just a given. So if you're doing a clinical study and you're randomizing,
there's going to be the same numbers on each side.  
But, generally, it's the same organism that's in the  
endotracheal tube aspirates. So I think endotracheal  
tube aspirates are still important, but it doesn't  
tell you exactly -- it gives you, I think, what the  
likely bacteria is, and I would accept that as the  
bacteria that's probably causing the biofilm.  

Is that what you were asking? But the  
problem is I think biofilms are a whole different  
world. The bacteria they -- for antibiotic  
penetration, the biofilm is poor, trying to clear the  
bacteria from biofilm. That's why I'm saying the  
numbers, if you're looking about what's happening in  
the lung, and if you can decrease it by two or three  
logs, you may not be able to clear the bacteria out  
of the lung. But even dropping a log of bacteria in  
the lower airway may be effective in improving the  
outcome of the patient. That's how I would look at  
it.

DR. MOORE: Dr. Rex, you had a question.

DR. REX: I actually have two, one for  
Drs. File and Craven and one for the FDA.
My first question goes to the issue of that initial dose of a non-study antibiotic. There was a comment made that there is a strong desire to give something quickly because we know that each minute, each hour's worth of delay is bad news.

That could be interpreted to mean that that initial dose has such an enormous effect that it cannot be discounted. The alternative view is that that initial dose is actually just that, it's the initial dose in a series of doses, and what's actually efficacious is the whole string of doses.

I suppose one way to get at that question would be to ask what would be the effect of one dose. If all you gave for somebody for HAP/VAP was one dose and stopped, would that be meaningful, efficacious therapy? We saw data yesterday for CAP that suggested that one dose might actually have more of an effect than you believe.

Is it the case that HAP/VAP is like that, or is it the case that one dose for HAP/VAP is, well, that's just the first dose, and it actually doesn't do very much?
Have you got any thoughts about that one?

Because that's going to become important. Allowing a single dose of something may turn out to be one of the critical facilitators for working in this area.

DR. CRAVEN: I'll jump on that one. Certainly, for CAP, CAP is different than, I would say, VAP. But I would say one dose would not make a difference. When you're talking about logs of bacteria, no one dose of any antibiotic is going to drop that to zero and basically have improvement. I think it could drop the bacterial count some, but I don't think it would have an effect. I don't think it should be a deterrent.

It's important, because some of these people also have secondary bacteremia. So if they have secondary bacteremia, that initial dose early can prevent sepsis, bad outcomes. So that's why the idea is to try to cover until you have some idea, is it the same pathogen that you think it is or is there a different pathogen, or is the site of infection in a ventilated patient -- it may be that they have a catheter-related bloodstream infection from a
catheter or another source, gall bladder disease or
intra-abdominal sepsis or another thing.

So a lot of time, you don't know. So if you
don't know, I think we should try to cover the
agents, and when we get smarter at 24 hours, try to
reassess the antibiotic therapy. I would say I would
not throw a patient out of a study because they got
one dose of an antibiotic. Otherwise, it's going to
be hard to recruit anyone to actually be in a
comparison study between two antibiotics.

DR. MOORE: Dr. File?

DR. FILE: Actually, when I presented the
possibility of sort of a microbiologic response and I
showed the difference between the responders and non-
responders as far as the bacterial load dropping,
actually, I found three papers that actually looked
at serial quantitative cultures after initiating
therapy. Now, they weren't in clinical trials,
but -- well, actually, one of them was in a clinical
trial. It was in the linezolid versus vancomycin.

But my point was if you looked at
collectively these three, they all had sort of the
same message, that if you look at the pathogens associated with the VAP, such as MRSA or staph aureus, for that matter, enterobacteriaceae, pseudomonas, you did not see a significant rapid drop with their first serial quantitative culture after initiating antimicrobial therapy, whereas you did tend to see a significant drop in some of these, maybe a cath pathogen such -- and I hate to say this because of what I said yesterday about allowing antibiotics, but they did show that for pneumococcus haemophilus, for example, there was at least -- and this isn't just after one dose. Usually, when we're talking about these serial quantitative cultures, they were done maybe 48 hours afterwards or 72 hours afterwards.

DR. REX: So how long did it take, on average, to see a reliable 1 or 2 log drop in your data for HAP/VAP? Can you give us a number on that?

DR. CRAVEN: First of all, it's extremely complicated, because it really depends on the organism, it depends on the antibiotic, the dose, is there combination therapy given. I think it's very
complicated, and these patients, we don't really know a lot. And we actually have looked at certain patients. Certain patients that have been on treatment for a while don't go down before they're completely cleared. They still have levels 10-to-the-2, 10-to-the-3, and some of them have a very slow drop over a period of time. It depends.

There's a whole set of host factors that we have no idea about. We don't know about their immune system, how they're able to clear the white cells, the macrophages, the antibodies, the complement. Older people don't clear as well. If they've got diabetes, they don't clear as well. If they've got renal failure, they won't clear as well.

So this population is extremely complicated, and I don't think we -- we know about one-tenth of 1 percent of what we really need to know for looking at response to therapy and what all the variables are that go into response to therapy.

I think it's very complicated. I wish it was simpler, because then you could design a trial and have a plan that you could probably execute. But
there's tremendous variability. Even the patients in
the ICU, there's a whole spectrum. Looking at APACHE
scores, you can have a low APACHE score, you can have
a high APACHE score, and there's a whole spectrum of
people. Some have surgery, some have wounds, some
have five catheters in, some don't, et cetera.

    DR. REX: May I be permitted, my question
to -- thank you -- my question to the FDA?

    DR. MOORE: Yes.

    DR. REX: Okay. So your sample
sizes -- this goes to Drs. Komo and Laessig -- are
based on what I view as an optimistic presumption
about meaningful pathogen recovery rates. And so if,
for example, I look at the recent experience from the
doripenem trials, the rates of recovery -- the rates
of accrual of patients who both had a pathogen and
met other criteria for being actually usable in some
sense would have been for their Gram-negatives, and
that study would have been closer to 60 percent than
70 percent.

    If I look at the recent televancin
experience, I get about half that, which is
30 percent. And those have enormous impacts on
clinical trial feasibility. If I look at this
concept of take -- even some of the worst case
scenarios here, your options 3 and 4, which are not
feasible on the face, but if I were to study staph
aureus, I'm now talking about 5,000 patients for a
clinical trial program.

Have you given any thought to ways to crack
that puzzle? Because that's going to -- if we leave
it as it stands, we can't do the work.

DR. MOORE: Dr. Laessig?

DR. LAESSIG: I'm sorry. Could you restate
that a little bit for me? I got the first part that
you thought our estimates were optimistic, but the
second part.

DR. REX: How do we deal with the
consequences of the fact that the rate of usable
patients is perhaps more like 60 percent for
Gram-negative pathogens, 30 percent for Gram-positive
pathogens? And if I want to ever develop a narrow
spectrum agent for pseudomonas, which a lot of people
ask me for, the rate is going to be more like
10 percent.

Have you got any thoughts about how to approach that in a realistic, non-geological timeframe?

DR. LAESSIG: I would say that we have not had much internal discussion about that at this point, I mean, because we did generate the numbers that we did. I don't know, Ed, if you want to jump in on that.

DR. COX: It's a difficult problem, John. How you actually solve that problem is not entirely clear. Are there certain ways you could try and enrich? I mean, you'll send up screening a lot of patients. Diagnostic testing probably isn't there in order to be able to get you to that population.

It is something that we're interested in hearing views on, too, I mean, if there are ideas and ways to approach this problem, because for particularly resistant Gram-negative rods, a new agent that offers therapy there could offer real public health value. The question is how do we work through this problem of a more limited spectrum
agent? It's a tough question.

So I certainly welcome thoughts and ideas from anyone on this, and we'll keep working on it, too, to try and figure out approaches that will allow such agents to be studied.

DR. REX: Are you open to strongly different approaches, approaches that deal with small numbers of patients and very high quality data? Are there approaches that could get us to there, or are we going to be stuck with sort of the traditional large clinical trial program? And separate out safety database, which obviously may have to be dealt with in a different way. But imagine a narrow spectrum anti-pseudomonal, which there -- I'm aware of a company developing it, what amounts to a monoclonal. And so it looks like it might very well have some utility, and, yet, how, how, how would you develop it?

DR. COX: And I think if we look historically at how the trials that were -- the overall sort of HABP/VAPB design that we're talking about here today, and you look back and when this was
developed, the types of agents that had been studied, these have typically been broader spectrum agents.

So this whole trial design concept I think is more derived from -- built around the idea that you've got an agent that has a fairly broad spectrum. So I think you're raising the important question of what if your agent is very different and much more narrow in spectrum? Then, yes, this approach may not be the right approach for studying such a drug, and we may need to figure out new approaches, alternative approaches, that would allow us to study a small molecule antibacterial drug that is essentially akin to like a monoclonal antibody approach, if you will, something that has a more specific therapeutic spectrum. So if it's just one particular genus, that makes it much tougher.

DR. MOORE: Ed, I think your point is well taken. I think there are historical precedents for, for example, the introduction of vancomycin for the treatment of MRSA, where that, my recollection, wasn't necessarily subjected to open clinical trials in the setting we have here.
The idea of these discussions is designed to -- and correct me if I'm wrong, but it appears to be primarily the supposition, the presumption that effective antibiotic therapy is currently available, and here we have a new agent that's going to enter that market rather than a setting where we have nothing available and there's a new agent that needs to be developed urgently.

DR. COX: Thanks, Tom. Yes, that's helping me think a little bit more on this issue, too, and the issue of particular trial designs. And we talked some about this idea of unmet need, and I think it's an area where we need to develop thoughts a little bit more; could you do an add-on design or something like that.

It's still going to be tough if there's low frequency of a pathogen of interest. An add-on design, you essentially show improvement. That's still going to be hard. But I think there are ways to think about trial designs that will be informative, that will be probably quite different than a trial design that's based upon an agent with a
broader spectrum that's intended for both empiric and
pathogen-based therapy.

John, it looks like you had some other
comments, some other thoughts.

DR. REX: The thought experiment that I'd
offer is that if we could come up with a way to do
the narrow spectrum anti-pseudomonal agent -- and
maybe it's not even a trial design. Maybe it's
program design that we're getting at. Imagine you
had an approach that was acceptable. Then, actually,
you could, if you needed to or wanted to, then a
somewhat broader spectrum agent could apply those
principles to some form of demonstration of activity
for e. coli, klebsiella and protease.

It strikes me suddenly that maybe we have
not spent enough time asking ourselves what would be
the approach. And there's been a lot of discussion
about pathogen-based approval kinds of approaches.
I'm not saying that's necessarily the answer, but
there's that kind of approach. There's some highly
instrumented patients, things where you really look
very critically at early microbiological response as
a likely correlate of outcome, like some of the continuous sampling of sinuses studies that have been done to examine the effect of therapy on acute sinusitis. Maybe there's a comparable approach here.

But the pseudomonas thing has really been bothering me because I'm aware of approaches that are narrow spectrum, and I have to say to those folks, "Guys, I don't see how you're going to do it." But it occurs to me now that maybe we should spend time on that.

DR. CRAVEN: Could I make a suggestion on that? I think if you're looking at ventilated patients and your culturing pseudomonas on day 2, and you're following that person over a period of time, that person may not get up to a level where they're going to have it. But if you're looking like it is pseudomonas antitoxin-3, because that's something that's as lethal anti-toxin, that strain that produces it, you could actually do that looking for pseudomonas selectively and in the tracheal aspirates when a person is intubated, like 48 hours after they're intubated, 24 hours, because there will be
organisms there. Generally, those organisms will continue to escalate over time.

So if you're growing pseudomonas on day 3 and you want to look at an intervention to try to reduce pseudomonas colonization, I think you can do it with surveillance cultures if you're looking at intubated patients, because you have access to what's going on in the lower airway.

So something like that I think is very doable if you're able to have cultures, follow the patient, and decide when you want to intervene to test product A versus product B. I think that's quite doable. In fact, there were earlier studies that were actually done looking specifically, targeting pseudomonas that could be done that way.

DR. MOORE: All right. Thanks.

Dr. Fleming, we're finally going to get to your question. Now, it's coming up on -- we're at time for a lunch break. We're going to take Dr. Fleming, Dr. D'Agostino, and Dr. Wiedermann's questions, and then we're going to have to end it there and break for lunch.
DR. FLEMING: I have a question for FDA, but I'd like to quickly touch on two of the issues that we have talked about already today, two key issues. I think John Rex was just bringing up a bit ago the question about one dose and do we have evidence that it's not enough.

I certainly concur that our HAP/VAP challenges today are more complex than they were in terms of prior treatment and concomitant meds than they were in the CAP discussion yesterday.

The issue that we have to deal with, though, is more complicated than whether we can dismiss whether one dose is enough. What we're really going to be talking about is what is the evidence for the effect of our antibiotic regimens, and the evidence is powerful. The effect is, by estimate, up to a 40 percent reduction in absolute mortality, with confidence that it's at least 20 percent. That's in the context of historical evidence against no effective antimicrobial treatment.

So the real question that we have to ask is, for those active comparators that we know are very
effective, how much of the effect is left when you
give not just one dose, but you give whatever the
pretreatment regimen was and the concomitant regimen
is, and that's a tough question.

Let me touch on one other thing for which
there was a lot of discussion earlier, and that's the
issue around risk differences, versus relative risk,
versus odds ratios. And the comments that I'm going
to give here are really focused on -- I don't think
the critical question to spend a lot of time on is
should we do a relative risk or an odds ratio. The
distinction here, and I think it's what Ralph was
saying, is the risk difference approach versus either
a relative risk or an odds ratio.

In essence, the FDA's data that they put
together has shown that we're reducing mortality in
VAP from maybe something in the range of 60 percent
down to 20 percent, where we have an estimate of
40 percent with confidence that it's at least
20 percent; and, hence, they have the 10 percent
margin that they've given to us on a risk difference
if the baseline rate is 20 percent.
John Powers and I, some time ago, I guess back in 2008, published in CID an extensive study on 7,000 patients in CABP, C-A-B-P, back in the '40s and '50s, to look at what was the effect of antibiotics against no specific treatment. And we were able to characterize patients into bacteremic yes versus no and age ranges; the youngest patients 12 to 29, 30 to 49, and above 50. So we created six cells.

In essence, what we found is the three cells where you're bacteremic, whatever your age is, or the non-bacteremic elderly patients, actually have results that look fairly similar to what we see in VAP. We're reducing about 60 percent mortality down to 20 percent, where the confidence is it's at least 20 percent delta with a margin of 10 percent.

The interesting thing is, though, when you looked in this setting at non-bacteremic patients who were younger, the antibiotic mortality was 7 and a half percent in the 30 to 49 group, but the effect size wasn't a reduction of 40 percent. In the no specific treatment group, it was only, by confidence, about 7, 7 and a half percent higher.
If you look at the youngest people, the 12 to 29-year-olds were on antibiotics, non-bacteremic, it was a 2 and a half percent mortality. If you compare to no specific treatment, the absolute increase was only, by confidence, at least 4 and a half percent higher.

So if in that group, if you had used a 10 percent margin in those non-bacteremic 12 to 29-year-olds, basically, what you would have been saying is, on antibiotics, it's a 2 and a half percent mortality, we're okay as long as it's not a fivefold relative increase, which is coming back to some of the things that Ralph was talking about. In fact, if you did that, you would have a statistically significant excess in mortality of 2 and a half against 6 and a half, if you had 320 per arm. It would be statistically significantly increased, tripling in estimate, but you'd still satisfy a 10 percent margin.

So, clearly, the 10 percent margin concept is not robust across all rates. In essence, though, what was robust was an odds ratio of 1.71 or 1.7-ish.
If you used an odds ratio of 1.7, you were able to get evidenced-based justified margins that apply to all age levels and all bacteremia statuses.

So from my perspective, the real attraction to the relative risk or odds ratio approach here is that once you get into lower or higher event rates than you're projecting, it's a robust result. So if you were projecting a 20 percent and you had a 5 percent mortality, that 10 percent absolute risk difference wouldn't be justifiable, but you'd be robust with an odds ratio difference.

So, in essence, that's the fundamental issue here that I think is to be considered. Most disease areas are, in fact, looking at treatment effects on a relative risk or odds ratio scale rather than a risk difference scale.

In terms of risk difference versus odds ratio, to me, it doesn't deserve a great deal of attention. I think there are some statistically better properties of an odds ratio. You could be doing logistic regression, for example, as you're adjusting for covariates. It's probably, I would
say, statistically widely used. But the fundamental
collection there is the risk difference concerns
versus using an odds ratio or relative risk. And the
1.7-ish range is what evidence base we could justify
was a robust justifiable margin, independent of
whether you were young, middle aged, old, bacteremic
or not.

   The question that I --

   DR. D'AGOSTINO: That's why I prefaced my
question, my example, where we were thinking of a
50 percent control rate, and it turned out to be a
30 percent. It threw the whole thing off.

   DR. FLEMING: Exactly.

   The question that I had was this HAP/VAP is
different, as we clearly know. We need this meeting
today independent of the meeting from CAP yesterday.
There are setting we have where there is a clear
unmet need. We talked earlier about lack of effect
against multi-drug-resistant pathogens. If you had a
HAP patient with Gram-negative rods, there is a need
for effective therapies in this setting.

   I think the agency, I believe, touched on
this and talked about the concept of superiority trials in such settings, which, by the way, get around all of these other issues of complications that we have as to whether or not somebody is on prior or concomitant meds.

Has the agency thought about this to a greater extent? I know it was put out there as one option, and it makes sense to me to consider in a setting where we already have emerged where there is resistance or inadequate effect of our current agents, that it isn't just we want something else that's non-inferior that can be there in the future. We need it today.

Is there plausibility to being able to, as another option here, do trials that would address today's unmet need in a superiority trial?

DR. COX: So that is something that we are working on. It's also been an interest, too, of folks at the IDSA who actually submitted a concept paper to us on this very topic, and it was part of the discussion -- I think it was the July 2010 workshop. And it gets to a conceptual approach where
if you're faced with pathogens where a new agent may be actually able to beat standard of care therapy, that may be a setting where a superiority design is a potential way to study such a drug and could show evidence of efficacy by essentially -- the new agent can show superiority to the standard of care regimen.

Another potential approach would be an add-on approach where you give standard of care in both arms, you add the new agent on and show superiority in a patient population where the new agent would presumably add something.

These would be probably challenging trials to do because patients would be probably quite ill. You'd also have to target the patient population of interest, and the number of patients that you might have that would be eligible for enrollment would also probably be a limited group. There may be certain epidemiologic risk factors that might help to guide you to the correct patient population. And then beyond that, too, it sounds like this is clearly a setting where you'd want to have a DSMB to follow the trial as it went along to make sure that the results

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weren't getting out of balance to the point that
you'd want to stop the trial based on the results you
were finding.

But I think this does provide a way to -- or
could provide a way to study a new drug that would
add. It's probably a fairly select agent that would
fit in this scenario, and I think there are still
significant challenges in such approach from a
practicality approach. But it is another option, and
it is one that there is interest in. So we've been
working away, and it's something that we hope to have
more information out there soon on.

DR. MOORE: Thank you.

We really need to break for lunch. Dr. Rex,
if it's a short response, that would be fine.

DR. REX: Very responsive.

Tom, speaking for my industry colleagues, we
have -- the idea of superiority, you're right, it
would be lovely, and it would simplify so many
things. And so a lot of effort has gone into the
question of how could one actually do that.

So here I'll speak for my company, where we
have spent a lot of time trying to figure out how to do that, and we can't find a way to do it that meets any requirements that anybody thinks are feasible. You might, under some remote circumstances, beat up on colistin once with one drug, maybe, if you could get the patients, and they would be wildly pre-treated with other things. They would have -- for the first several days, they would every antibiotic known being given to them on both arms of the trial because everybody is in panic mode about this person.

So you end up concluding it's really hard to do. But even if you did it once, our real problem as a community is I need to do it 10 times. In truth, we need 10 antibiotics. That's the idea. Say it's 10 by 20; we need a bunch of them. And you're only going to be able to use the superiority by beating up on the fact that there's no available therapy maybe once or twice, and we will not have an approach for industry as a whole. And betting on superiority when it doesn't make good biological sense is not a viable business strategy that I can get anybody to buy into.
So I wish I could. The answer is we've tried, and we don't know how to do it.

DR. FLEMING: The idea here is not as a whole. It's not the only way. It's, is it an option that would apply in settings where we already are at the point where we have an unmet need with resistance, and here are people that when you beat them up with everything, those things aren't addressing the bug, and we have something that may and this is superiority.

So it's an option that wouldn't suffice for all settings, but it could be something that would be a straightforward approach in some settings.

DR. MOORE: Okay. All this talk about dropping a log of bacteria has made me hungry, so we'll now break for lunch. We'll reconvene again in this room in -- actually, let's make it 1:05. We'll get a little bit of wiggle room.

Please take any personal belongings you may want with you at this time. Committee members, please remember that there should be no discussion of the meeting during lunch amongst yourselves, with the
press, or with any member of the audience.

    Thank you.

    (Whereupon, at 12:13 p.m., a lunch recess was taken.)
AFTERNOON SESSION

(1:08 p.m.)

Open Public Hearing

DR. MOORE: Okay. If everyone could take their seats, we'll get started here very shortly.

We'll get started with the open public hearing.

DR. MOORE: Let me start off with this statement. Both the Food and Drug Administration and the public -- by the way, thanks to everybody for coming back. I know it was a short lunch. We still have a lot to cover. Anyway, thanks again.

So both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of
any financial relationship that you may have with any company or any group that is likely to be impacted by the topic of this meeting. For example, the financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA in this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and
treated with dignity, courtesy and respect.

Therefore, please speak only when recognized by the chair. Thank you for your cooperation.

With that, our first speaker will be Dr. Shlaes.

DR. SHLAES: Well, thanks again for the opportunity to speak to you today about trial design requirements for HABP/VABP.

My name is David Shlaes. I did speak to you yesterday. Let's see if I can make this work, try that. Okay, good. I do consult for the pharmaceutical industry. I have a large number of clients. I didn't list them all here, but you can look at my Website if you want to know who they are?

I am an Infectious Disease Society member. I did participate in drafting Bad Bugs, No Drugs, and the opinions I am going to express today are my own. I did have a 16-year career as an academic physician-scientist, and my area of work was antimicrobial resistance. I have now spent 15 years in industry, so I've had a fairly long career working on antimicrobial resistance and antimicrobial product
discovery and development.

So we do need a strong -- I believe we need a strong, vibrant, scientifically-based, interventionist, FDA, to assure that we have efficacious and safe drugs. I believe we also need to help combat infections caused by resistant pathogens, a robust pipeline of new antibiotics, and, at least for the indication on the table today, these two concepts remain mutually exclusive.

Twenty-eight-day mortality in the context of these trials, I believe, regardless or in spite of what's been said earlier, and with respect, is a confounded variable, or at least it confounds me, because it depends so much on all the other comorbidities that these patients have in addition to the pneumonia that’s under question.

A more appropriate endpoint based on clinical outcomes could easily be justified using pharmacometrics. So one could establish a treatment effect or M1 using pharmacometric methods and derive from that M1 an appropriate M2. And we could do this in the context of modern trials that have already
taken place without having to rely on a historical record of retrospective and observational studies.

The 20 percent or higher mortality rates required and the approach using an 80 percent power to keep sample size down increases sponsor risk, the 10 percent margin is much too conservative, and the odds ratio method makes things worse as you decrease the mortality rates, at least in terms of sample size. The M1 is already based on a 95/95 -- what I call 95/95 discounting. But that M1 that's calculated for this margin uses inappropriate therapy or delayed therapy, that is, delayed appropriate therapy, and it's not NO therapy. And, therefore, the set points are already conservative. There's no reason, in my view, to do the 95/95 discounting.

I think the possibility to carry out a single trial in VABP is attractive, but I don't know why we're doing this to ourselves. Virtually all patients in the ICU and 60 to 80 percent of patients in hospitals for any length of time receive antibiotics at some point during their stay. So I don't understand why we are trying to limit our
trials only to outlier patients compared to what we usually see in clinical practice.

We actually want to enroll patients with prior treatment into our trials, such that we can study patients who are more likely to have resistant pathogens. And as we've already discussed, there are no clear data that suggest that patient outcomes are affected by prior antibiotic use anyway. This is an area of particularly high and urgent medical need, and I think that we cannot make it impossible for us to get the drugs approved for American patients.

The number of ongoing phase 3 trials for new antibiotics in this indication is zero. But there are several new drugs on the near term horizon for phase 3 trials, I would say within the next year or so. So I think going forward, the way to get there to start with is to declare an immediate moratorium on implementation of the 2009 draft guidance and go back to previous guidance while awaiting something new. This will eliminate the proscription against prior antibiotics, as well.

We can then use pharmacometrics to define an
M1 and derive an appropriate M2 to allow a nosocomial non-inferiority margin for clinical outcome at test to cure, which I think is a more appropriate endpoint, or as PhRMA has suggested, clinical outcome plus being alive at 28 days is perfectly reasonable.

The European Authority has allowed 15 to 20 percent in those non-inferiority trials, with the primary endpoint of clinical outcome of test to cure, and they are willing to discuss the use of pharmacometrics.

So I want to show you some data that you probably don't see very often at an FDA AIDAC meeting. These are antibiotic sales data, and they're going from the years 2006 to 2010. And the North American market is shown in red, and it's around $10 billion. Asia Pacific, outside of Japan, has already surpassed the U.S. market, and emerging economies, in general, have certainly surpassed the U.S. market as of 2010, and this is going to increase. Those markets are going to dwarf the U.S. market in years to come.

If we do not provide a regulatory pathway
for new antibiotics in the U.S., Americans will be deprived of new antibiotics for key indications other than off-label use, which, by the way, will be paid for by Medicare and other payers. The U.S. market for antibiotics will further be marginalized, putting Americans in a take-it-or-leave-it position for new antibiotics. In other words, the antibiotics will be developed elsewhere under guidance from other regulatory authorities, and a data package will be presented to the FDA in a take-it-or-leave-it fashion.

Companies will shift their focus overseas, leading to a U.S. innovation drain. This is already happening, to a certain extent. So I'm asking you not to let this happen by providing feasible and reasonable pathways to get drugs approved for this indication.

Thank You.

DR. MOORE: Thank you, Dr. Shlaes.

Our next speaker is Dr. Hong.

DR. HONG: Good afternoon. My name is Zhi Hong. I'm the head and senior VP of the infectious
disease unit at GlaxoSmithKline. I have the global responsibility for the infectious disease R&D from target through submission to post-marketing support.

So our society critically needs new antibiotic due to the emerging penem-resistant bacteria passage in the recent docket. And physicians all over the world face life-threatening infections, which limit our new options.

We all know the critical contribution of effective antibiotic therapy in the past. We have to do something now. However, all the stakeholders must recognize the unique paradox in developing antibiotics. The high public health need versus the low regional investment, the proper use of new antibiotics versus commercial performance, often incentivized on volume used. We coexist in this very complex environment. We have to help each other to prevent further tradeoff made at the expense of the public health or irresponsible use of new antibiotics.

In our industry, GSK and many other companies have and will continue to commit to address
public and global health issues. As a company, GSK has a longstanding legacy in infectious disease medicine that saves lives, reduces suffering, and diminishes the global burden of infectious disease. It is an area that we wish to continue to invest to address the future need of the global community.

We currently have four clinical stage compounds in development: adjuvant zanamivir, which is in phase 3 for hospitalized influenza. But I'm here today because we have three very exciting completely novel mechanism-of-action antibiotics, all of them in phase 1/phase 2 development, for treating serious infection in the hospital.

As you can imagine, for an organization like GSK, we carry significant development and financial risk in the face of regulatory uncertainty. In a time when medicine development is a global activity, regulations can have profound impact on a company's ability to deliver medicine access to patients. I think FDA has the opportunity to lead the way for the rest of the globe so that critical medicines, such as new antibiotics, will become readily available to the
U.S. patients in a very timely manner.

We must reflect that patients' lives get saved because science and innovation is rapidly translating to medicine. Patients' lives get saved because our stakeholders, public and private, are willing to work in synergy, as exemplified by how we work to address the HIV/AIDS epidemic and our continuous collaborations through the Forum for Collaborative HIV Research. Patients' lives get saved because physicians and health care providers are better educated about the new medicines and are willing to use them properly. Patients' lives get saved because payers are willing to reward innovation based on value and provide critical access to medicine.

In our business, both for the regulator and the industry, nothing is a hundred percent certain. From the discussion yesterday and today, I am hopeful that we can quickly come to agreement so that we can practically generate a sufficient body of evidence and establish feasible standards of benefits that will allow us to efficiently demonstrate the value of
new antibiotics against resistant pathogens.

So together today we have the responsibility to tackle the emerging health care crisis, and having no new antibiotics may be the greatest risk to our society.

I thank you for your time.

DR. MOORE: Thank you, Dr. Hong.

The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments.

Before we go to Dr. Cox's charge to the committee, we ended the last session with a couple of unanswered questions.

Dr. D'Agostino, we'll start with you. Did you still want to ask your question from last session?

DR. D'AGOSTINO: I do have a question. I can hopefully make it quick. I was thinking about these trials with mortality as the endpoint, which I
concur with, and I was wondering, in terms of this one trial versus two trials, if you were talking about superiority trials. And you said you have to have two trials. Once you have one positive trial, nobody's going to go into the second trial. Here's a non-inferiority, so it's a little different.

But I'd like some maybe response or discussion from PhRMA to respond to the question.

The one trial versus two trials, is the one trial more attractive because of the -- certainly, you only have one trial to do, but also the concern that if you were going to two trials, you may get in the bind that after the first trial comes out, they won't be running simultaneously and published simultaneously. After the first trial comes out, the second trial may be very hard logistically to put together.

Has that come to any of the discussions that PhRMA has had?

DR. MOORE: Dr. Fromtling?

DR. FROMTLING: Yes. I think the advantage of one trial is that certainly it's easier to manage.
Trying to do two trials, even if they're similar design, adds a lot to the complexity of trying to get the trials completed, recruiting sites and such.

So the one trial is attractive, and we are still talking about large patient numbers. That's still a bit discouraging, but we'll have to see where that conversation goes today with regard to how the statistics will be applied.

But I do agree with you that if one trial is moving along quicker than the other, and your data coming from that is very positive, it makes recruitment in the second trial more difficult. So there is a lot of attraction to the single trial. As I mention in my presentation, that's really a significant step forward to be able to look at these drug trials in that way.

DR. MOORE: Thank you. Dr. Wiedermann?

DR. WIEDERMANN: Yes, thanks. I just wanted to not necessarily ask you a question, bring up a point that I think we've talked around a little bit and want to make sure it stays in the discussion with the whole issue of concomitant potentially effective
I think in the PhRMA presentation, the statement was made, "We believe that permitting 24 hours of other empirical therapy is essential to successful recruitment," but I think it really goes beyond that. And some of Dr. Laessig's data, although it is from non-approved drugs, showed that patients were on several days of other therapy. I think that even in a sort of vigorous, de-escalation mode, it's unlikely to happen before 48 or 72 hours of therapy, depending on how sick the patient is and what the risk benefits of drawing back on de-escalating therapy when you still don't know the final culture results.

So I think we just have to be aware that we're talking about trying to analyze data when we may have a number of patients on two or three days of sort of overlapping therapy with whatever the study drug is.

DR. MOORE: Thank you. Dr. Shyr?

DR. SHYR: So I do have a question for Dr. Fromtling. So when you say -- it's an
interesting idea. You say you want to do 28-day mortality-plus. Now, your target is 70 percent success rate. Did you review any data like FDA reviewed, and your 70 percent comes from the data or does it come from assumptions?

DR. FROMTLING: I'm not able actually to answer that directly with regard to data analysis. I know we've had a lot of discussion in our group as we were preparing our slides for this, and we were just trying to look at different success rates in order to estimate what patient numbers and statistics would best apply.

DR. MOORE: Ms. Young, you indicated before the break you had a question you wanted to ask.

MS. YOUNG: I was just curious. When Dr. Rex had asked the question about the impact of the one dose, was your answer related to the VABP patients or the combination? I don't know if someone from IDSA is here.

DR. MOORE: Dr. Craven?

DR. CRAVEN: Sorry. I didn't quite get the question. You were asking one dose in terms of VABP?
MS. YOUNG: I'm just repeating Dr. Rex's question and asking if your answer was applying to VABP patients, or to a combination, or would it be the same answer for HABP alone.

DR. CRAVEN: I think it would probably be the same for both patients. The difference is that with VABP, at least you know the organism for HABP. If you don't have a sputum culture, then it's hard to know what it would be. But I think it would probably apply to both, but I was talking about VABP.

DR. MOORE: Okay. Let's move on then to Dr. Cox.

Questions to the AIDAC and AIDAC Discussion

DR. COX: Okay. Thanks Dr. Moore.

So we've got four questions that we'd like to get the committee's advice on, and they're all discussion questions. And we've had a lot of good discussion. I want to thank all the speakers today who provided comments and information.

The first question, please discuss the merits and limitations of the single trial plus supportive information proposal for hospital-acquired
bacterial pneumonia, ventilator-associated bacterial pneumonia, and please discuss the types of supportive evidence that would be considered acceptable if only a single HABP/VABP trial is conducted.

Again, I mention the options provided in the background document is sort of a starting point for the discussion. You certainly can react to that and/or other ideas that you may have.

On Scott's slides, they were numbered 1 through 4. Numbers 3 and 4 are actually embodied in number 3 in the background documents, so just for -- they're still the same options, in essence, that are embodied in both places there.

The next question is question number 2. Please discuss if a non-inferiority margin of 10 percent will be acceptable if the active control mortality rate is less than 20 percent; and please discuss if the odds ratio or risk difference metric is preferred when the control mortality rate is less than 20 percent.

Number 3 goes on to the question of timing of an all-cause mortality endpoint. Please discuss
the preferred timing for the all-cause mortality endpoint. Would an assessment at an earlier time point be preferred to the 28-day assessment?

These are discussion questions. If there are other thoughts on endpoints that you'd like to mention, number 3 probably seems like an appropriate opportunity to do so.

Number 4. Please discuss the following scenarios regarding the use of prior antibacterial drugs. The A question, if empiric -- and we flipped these from the background document, so you noticed, they're a little bit different in order, so just to anchor folks in that.

A deals with if empiric antibacterial treatment for HABP/VABP has begun prior to enrollment in the trial, what duration of therapy would be acceptable and unlikely to confound interpretation of the treatment effect of the study drug. Please describe your rationale, and please discuss if there's any other information that might be useful to further address this question.

Then the B part: Should a patient who
develops HABP/VABP while receiving antibacterial
drugs for other infections be enrolled in the
HABP/VABP trial and, if so, please discuss some
scenarios where this will be acceptable. Things you
might think of there might be culture information
that might become available at the time of the onset
at HABP/VABP, other therapies that the patient may be
on, whether they're effective or not, how long the
patient has been on therapy, those sorts of issues.
It would certainly be helpful to hear comments
related to that.

Those are the questions we have for you, and
we appreciate your discussion.

Back to you, Dr. Moore.

DR. MOORE: Thanks, Dr. Cox.

So as with yesterday, the most important
element in addressing these questions is, if you can,
sort of an explanation of your thought processes
behind -- the rationale behind your comments, that
will really help the FDA out.

Now, before we go to that, what I thought
we'd do is, with the first question, we'll go around
the table, unless there are some specific questions
about that we wanted to pursue.

    Before we do that, Dr. Rex, you wanted to
say something.

    DR. REX: Thank you. I'd like everybody to
take a minute to recognize the gravity of the debate
we're about to have this afternoon. Despite the
significant work on the part of the many, I really
must recognize and acknowledge that you guys at the
FDA have done a great job. Your compendium in your
briefing book is outstanding.

    I'm fundamentally concerned that after this
meeting, we're going to remain in a situation where
HABP/VABP cannot routinely be pursued in the U.S. by
drug developers. And so my comment to my colleagues
on the advisory committee is that it's really
important that we help find a tractable and flexible
path forward, and that's a problem that we need to
solve in a durable manner. We need to solve it
flexibly for broad spectrum Gram-negative agents, for
broad spectrum Gram-positive agents, for narrow
spectrum Gram-negative agents. We need to solve it
for drugs going into trials today, drugs going into
trials 10 years from now. We need a solution that
works when the mortality rate is 20 percent and when
the mortality rate is 10 percent, as it might become
with better supportive care.

I must note in passing the situation in the
U.S. with respect to work in these areas and contrast
the situation outside the U.S., where we have a clear
example in the recent approval by the EU of
telecuncin for nosocomial pneumonia that suggests
that other agencies who have thought deeply about
this matter have reached different conclusions. And
I'd like to see if we can understand how some of that
thinking might be brought in here.

I observed yesterday that the deepest
question for the AC is one of balancing public health
versus benefit for the decisions that must be made
even in the face of incomplete or imperfect data and
applying that to the evaluation of safety and
efficacy of new anti-infective drugs. And that's
language that I've stolen out of the IDSA's recent
letter to Commissioner Hamburg about this area.
We're not going to have the data we need, but we actually have to find some things that work.

This endpoint margin discussion we're about to have is one of the two most important ones, that along with prior antibiotics, and I think you need to -- it's a tough area. I have some comments that I'll make when it's my turn to make them about endpoints and margins.

But the key I really want to focus on is the need for flexible approaches that give us options for in the future. If we lock ourselves into a box, we may find ourselves unable to dig out of that hole as we go further down the road.

So that, I think, is a critical element of this. We're looking for thinking that works today and for thinking that works in the future. So that is a key theme. If you want 10 drugs, you've got to have a pathway that works for the first drug and for the tenth.

Thanks.

DR. MOORE: Thank you.

So why don't we do this? Let's start with
Dr. Reller. I'm going to start on this end of the

Dr. Reller: Which question?

Dr. Moore: Question 1.

Dr. Reller: Four was up there.

Dr. Moore: Sorry about that. I ran into

this problem yesterday. But this time we'll keep the

questions in order.

Dr. Reller: I am not keen about a single

trial, so that the question of the supportive

evidence to accept a single trial is relatively less

important to me.

There are some similarities between HABP and

VABP, but there are important differences. So I'm

more interested in, if I had to have a single trial,
in the ventilator-associated pneumonia, because I

think that's a tougher nut to crack, both in terms of
certainty of diagnosis -- the specimen may be easier
to get, but it's harder to interpret what it means.

And there will be opportunity for more discussion on

that later.

What would really be attractive to me, and I
don't -- it was alluded to, but I don't think listed as one of the questions -- is what the statistical implications would be in trying to keep reasonable numbers of patients, is to have a single trial that included both kinds of patients, but that there was certainty of having a very narrow range, ideally 50/50, maybe it could be 45/55, but that it would be split between the two, that would enable a separate analysis in a larger trial of possible differences between performance in these two kinds of pneumonia.

If the outcome was similar and one had the advantage of having the efficiency of a single trial, but you had substantial numbers of both kinds of pneumonia, I would think that would be the ideal situation.

I'll stop there, because some of the other, I think, important aspects that I would like to bring out or see brought out could easily come up in the discussion of the other questions.

DR. MOORE:  Thank you very much.

DR. FLEMING:  Thank you. I'm looking forward to the discussion. These are very complex
issues. I'd go back to what Dr. Cox set the context for at the beginning of the day, and that is we need to be very cognizant of the value of coming forward with approaches that are feasible, and I think Dr. Rex was just addressing that point; but as he also said, scientifically sound and ethical.

The objective here is to ensure that we're coming forward with proposals that will allow us to have interpretability, which is inherently very difficult in non-inferiority trials. And this is not just an artificial statistical or scientific requirement. This is about protecting patients. This is about ensuring that we're not just giving patients and caregivers a choice, but we're giving them an informed choice; that we, in essence, put forward approaches that we can, through evidence-based justification, be confident allows us to distinguish between therapies that are less effective versus adequately effective.

So one of the first issues here that we have to encounter is what is sufficient data when frequently, as has been articulated by many, there is
great merit to the concept of having adequate and well controlled trials, plural. So an ideal scenario, but obviously data intensive, would be to have one VABP and one HABP trial, as is put forward as option 3, in which case there wouldn't be a need for external supportive evidence.

I also endorse the concept that if there were two VABP trials, the logic of being able to extend that indication to HABP and VABP, to me, is sensible. I worry about going in the other direction, and I think the agency was careful to not do so in their options, to have HABP data only and extrapolate that to VABP, where, with the doripenem and tigecycline concerns, they seem to be most apparent, most significant in the more ill patients.

So the strategy, if there is an extrapolation, I'm much more comfortable with the extrapolation of establishing evidence-based justification of safety and efficacy in VABP and extrapolating that to a HABP setting.

So that then brings us to the possibility of doing single trials in these settings, either a VABP
trial with a HABP/VABP indication, or a HABP trial with a HABP-alone indication, where supplementary data would be important. And in those settings, several options were put forward.

I'm, in principle, supportive of this idea of saying if we have two trials where there are pathophysiological relationships in the disease process, that we can extrapolate. And so what's been put forward is the intra-abdominal infection setting, the skin infection. I worry about those, the first being so surgical-dependent, the second, daptomycin looked fine in skin. It certainly didn't look fine in pneumonia. The CABP setting seems, as what the agency has put forward as a possibility, if the drug we're studying here has broad spectrum activity that includes common pathogens in CABP, that does make sense to me as an option to go forward.

So I think it is appropriate to consider the option here for a single trial, particularly in the spirit, I would find, a single trial for a mortality endpoint with a proper non-inferiority margin, with very strong evidence that we truly have an indication
in that trial; that this agent is not inferior, is not losing an unacceptable level of mortality effect against active comparators, as strong evidence that would lead me to be more willing to consider a single study if it, in fact, is a VABP trial that could lead to then the possibility of an approval in both HABP and VABP, with then supportive evidence from a proper supportive trial.

DR. MOORE: Thank you. Dr. Fratzke?

DR. FRATZKE: I would go along with the common trial, having the two together. However, I am concerned about the pathogens. If they're both exactly the same, probably so. But even though, I think I would still want to keep them separated some way in the study, so that if there was any difference, I would want to see that. But I probably, eventually, would go along with the single trial, with that in mind.

DR. MOORE: Thank you, Dr. Fratzke.

Dr. Goetz?

DR. GOETZ: I also support the single trial concept. I believe that a study done in ventilator-
associated bacterial pneumonia -- I can't pronounce
V-A-B-P -- would suffice for giving us confidence
that the drugs would also be effective in the
treatment of hospital-associated pneumonia, and, I
dare say, many cases of health care-associated
pneumonia.

I think that some of the divisions and
dichotomies that we've set up amongst these entities
are really faults in nature; that the patients with
hospital-associated pneumonia oftentimes have severe
disease, warrant intubation, and are septic
physiologically in those regards. They not be
intubated as long, but otherwise resemble patients of
ventilator-associated pneumonia.

Similarly, persons with health care -- with
hospital-associated pneumonia oftentimes are affected
by multi-drug-resistant organisms, and, as has been
alluded to earlier today, are patients admitted from
nursing homes who have health care-associated
pneumonia who wind up in our ICUs and are to my mind
indistinguishable physiologically and in terms of the
organisms that they harbor from people with
ventilator-associated pneumonia. While it's been mentioned that we could perhaps have a study that melded the two populations, I fear that there would be statistical complications there, but I'll leave that to the statisticians to address. I think it's probably cleaner, therefore, to do the VABP study alone and to extrapolate forward.

In doing such a study, certainly the enabling data are very important. I think that having relevant animal models and showing that we have the right pharmacokinetic and pharmacodynamic principles is going to be an important aspect.

Other clinical trials, the aspects of intra-abdominal infections and skin soft tissue infections have been mentioned, I think it's very important to look here at the pathogen mix and severity of diseases, as well. The community-acquired pneumonia gives us a cleaner pathway, I think, quite frankly, were the drugs to be available. Going to some of those other pathways, we really have to look at severity and relevant pathogens, its non-inferiority study, with all of its aspects of making sure the
right patients wind up in the study, that we truly
have patients who have a high probability of
establishing a microbiological diagnosis, where we
have clear radiological data, and the clinical data.

It's in that regard, with all the challenges
that we face, standardization of the microbiology is
going to be an important aspect, and standardization
of other protocol aspects, particularly de-escalation
of therapy, so that we have a cleaner endpoint.

Then perhaps my final point is that if we're
going to do a single study, I think we have to have a
very statistically rigorous single study. And on the
FDA slides, they've suggested we have a study with
80 percent power, a study with 90 percent power. I
would favor having a better powered study in that
regard.

DR. MOORE: Thank you. Dr. Neely?

DR. NEELY: I also support the single trial
concept. I'll tell you why. I'm concerned from a
study standpoint, but applauding from a clinician's
standpoint, that my infection control officer at our
hospital, which is a pediatric hospital -- so I hope
that the adults are seeing similar trends that we've had -- something like a 70 percent drop in our VABP rate over the last couple of years, with the institution of measures like frequent suctioning, enforcing gowning and gloving for dealing with intubated patients and so forth.

So I'm concerned that if we increase the burden of sample size beyond what's going to be the discussion for question 2, we're going to have even more difficulty doing these studies.

So I do like the idea of a single trial with supportive evidence. I also think that it's probably better and easier to do it with VABP as the single trial.

In terms of what supportive evidence I think would be relevant would really depend, I think, also -- similar to what Dr. Goetz was just mentioning. I would look at the antimicrobial spectrum and the severity of disease. I think intra-abdominal infections are going to be an important one. I think those trials would have to be controlled for surgical interventions. That's a good
point. But I think the basis of supportive data should be based on spectrum and severity of disease.

DR. MOORE: Thank you. Dr. Follmann?

DR. FOLLMAN: I agree with the comments that have been made before. I think two trials is obviously more desirable, and in this setting, I'm willing to go along with the single trial in HABP or VABP, provided there's supportive evidence. I liked what was written in the FDA document regarding this, and I just wanted to comment about supportive evidence.

So I really think a single trial is sort of a dangerous thing that you should be careful about when you do. Typically, we require two trials, two independent trials, because this allows us to avoid the concern that one of the trials might be successful because of sort of a fluke, in some sense. And so the replication, the independent replication is very important.

So if you have a single trial just within HABP or VABP, and you look for additional clues within that study, that doesn't really satisfy me in
terms of independent replication or independent evidence. So if you have a sort of strange control group that has, say, a high rate, it might have other clinical outcomes other than mortality, which are also unfavorable. So looking at two different endpoints within the same trial I think can give you a false sense of security or replication or supportive evidence.

So that's why, for me, and has been discussed before and was put in this document, I think it's important to do another independent trial with humans and in related conditions, such as CABP, would seem to make the most sense to me.

DR. MOORE: Thanks. This is Dr. Moore. The way I see this is, as pay-for-performance initiatives succeed nationwide and there's increased public reporting of hospital infection rates, the rates of VABP are expected to decline -- have declined and are expected to decline further, as Dr. Neely mentioned. The same is true for HABP; thus making enrollment of patients even more difficult over time. So I think having a single trial is unavoidable, and I would
certainly be in favor of that as long as there's corroborative evidence from other sources, as was mentioned, clinical trials having to do with CABP or complicated skin and soft tissue infections.

I think it would be important to stipulate the minimum number of VABP, V-A-B-P, patients included in such a single trial and how many, of course, or what the relative percentage would be, I haven't the slightest idea. I'd have to defer to the statisticians there.

But I think that the reality of -- the biggest unmet need, as has been mentioned, in the near future, are the space or the escape bugs, specifically, multi-drug-resistant Gram-negative bugs. And we really need to facilitate as much as possible, while protecting patient -- providing for patient safety, the generation or the ease of creation of clinical trials and execution of clinical trials in the United States, where the microbiological need is different from that of the rest of the world.

Dr. Chatterjee?
DR. CHATTERJEE: Thank you. I would like to support what seems to be, so far at least, the majority opinion, which is to have one trial, well controlled, with the adequate number of subjects in it so that we would get data that would be solid and interpretable to us.

I'd just like to make the comment here that a lot of the discussion that I've heard today and from my reading of the background materials seemed to me like we are trying to make the perfect be the enemy of the good to a certain extent in this situation. Clearly, we're dealing with two conditions that are killing people, children, as well as adults. We do not have the drugs or drug combinations that we need to take care of many of these patients, and this is a dire need at this time. And anything that we can do as a committee to encourage the FDA to move these trials forward quickly so that our patients have access to these life-saving drugs, in my opinion, would be needed.

Before I close, I'd just like to say a couple of words about including children in these
trials. I noticed in my reading of the background materials that there was a very tiny portion of them devoted to including children in trials early, and I would exhort the FDA to include a pediatric arm to any trial or trials that are conducted early in the process and not to wait, because our patients are as much at risk for these conditions as the adult patients are.

This would be particularly important for any new agents that are developed and combinations of older agents that are developed. PK and safety data in children are particularly important for us to obtain early, and these could be started before even perhaps efficacy trials are looked at or effectiveness trials are looked at.

Then one last word about post-licensure involvement. This is to my colleagues in PhRMA. And that is I know that the FDA has requirements for post-licensure studies, but I think this is a situation where those types of studies might give us additional information that would help us in the management of our patients.
DR. MOORE: Thank you. Ms. Young?

MS. YOUNG: Yes. I would support the comments that have come before, particularly Dean's comments in terms of, ideally, we should have two trials, because we're in a non-inferiority situation. However, given the difficulties, I think a single trial I would support, with very strong enrollment criteria and endpoints, because we are talking about the strong agents, hopefully, the strongest agents for the sickest population. So this is serious business. So I'd like to see a balance there.

I agree with the pediatric enrollment arm and post-licensure information, because this is a process that should change over the next few years with improvement in diagnostics, and we might not be caught in this situation that we are in now where we are kind of subject to some confounding variables no matter what you do.

DR. MOORE: Thank you. Dr. Weinstein?

DR. WEINSTEIN: I'm with the majority here. I concur with most of what's been said, and I have some of the same reservations that Dr. Follmann
raised about the issue of the preference to have two studies. But I think, as Dr. Reller said, if you could do a single study where you would include and then perhaps stratify analysis of the VABP patients and the HABP patients, that that might work. And similar to the comments of others, the corroborating evidence from another study, probably either community-acquired bacterial pneumonia or skin and soft tissue infection.

DR. MOORE: Thank you. Dr. Cappelletty?

DR. CAPPELLETTY: I also am in favor of a single trial. Again, I would like to see the data stratified, that the HABP versus VABP patients be separated out and provide individual responses. One of my problems with reading the recent paper that said treating patients per guideline had worse outcomes was they did not separate out those patient groups. And so I really didn't know whether we had mismatches in terms of HABP/VABP in each arm as to where the data really lie. So I think getting that separation, in addition to the overall, would be very important.
I'm less in favor of the additional data coming from a community-acquired pneumonia trial, because the microbiology is so vastly different in that arena. And we've seen drugs that don't have great activity still work really well with CABP, and so I would really hesitate with that.

I agree with Dr. Neely, I'd rather see similar microbiology in supportive data, so looking at similar spectrum from other sources. As a way to maybe compromise might be, as well, to maybe, in addition, do some pharmacometrics with these studies that are the pneumonia-based study, and maybe start to get some ELF concentrations and data to support the penetration issues into the area for that efficacy response.

DR. MOORE: All right. Thank you.

Dr. D'Agostino?

DR. D'AGOSTINO: As I was expressing earlier, I have concern that if you have one good trial, a second trial isn't going to be necessarily that easy to put together and operate. So I think my feeling is that one large trial that probably focuses
mainly on the VABP type of patients, where you can
make some inferences about the HABP patients, is
probably the way you could go.

    I think we have to be very careful that the
study should be big. There should be a 90 percent
power sort of in the cardiovascular arena, where one
trial is very much the norm in certain situations,
but they're big trials -- and the big trials are the
numbers sitting on these pages, not the 10,000 in the
cardiovascular. But they're big trials, and they
have good power, and well thought out. And not only
this idea of where do they extend to, but what do
they have; do they have broad representation; is
there consistency within the trial, across groups and
so forth. Not everybody reaches or every test
reaches a .05 with consistency, and the trial should
be designed to be broadly representative, and the
analysis should include a secondary type analysis.

    This idea of consistency, I think it's very
important that these trials have mortality as the
endpoint so that you do have a clean result at the
end. And for the further evidence, I've seen, like
in the cancer arena, where you have accelerated approval, then the trial -- the drug gets approved on that, and then the second trial that they'd like or some collaborative data is another indication, I think that can hold here. They can be doing these things simultaneously, or they can already have the collaborative evidence, and then wait for this big trial. But one big trial, one well solidly run trial, good representation, and then other evidence, supportive evidence, I think is a fine package.

DR. MOORE: Thank you. Dr. Bennett?

DR. BENNETT: I agree with the majority that a single trial seems the most practical approach. The question is, is it HABP and VABP or one or the other? I'm a little concerned about mixing the two together, because you might end up with disparate results. Then if I were the FDA, I would not know what to do with that information if the two portions -- there will be smaller sample sizes and less power to show they're different, but if it looked different, what would you then do?

So I would have chosen just HABP or VABP.
And then the question is, is comorbidity less of an issue in HABP? I don't know the answer to that, but my clinical intuition is it would be. I know in most intensive care units, the chance of walking out the door alive is 75 percent, which means a lot of people are dying in intensive care units of a lot of things, the point that David Shlaes had made.

So if the comorbidities were less of an issue, and I'm not sure they are, I would have picked the HABP over the VABP. Of course, patients who are hospital-acquired pneumonia that were ventilated would still stay in the study, I think that's intuitively obvious.

Now, what would be the supporting data? Pharmacokinetics is fine; pharmacometrics that have been mentioned here, but, basically, that relates back to MIC. And having done lots of MICs in my career, I know that if I want to make the MIC one tube higher or one tube lower, I can do that. Just change the media, change the inoculum. It's not true of every antibiotic, but certainly you can make a difference there.
So I have a deeply -- sorry, Mike Neely. I have a deeply engrained suspicion about how we would use the pharmacometrics to help support this. So I'd rather see a trial in the lungs, such as community-acquired pneumonia, or in deep tissue. I don't like skin and soft tissue infections for the support, because as Tom Fleming was mentioning, the role of surgery is so important in complicated skin and soft tissue infections. But I would like to see another trial in another site to support this, but I like the idea of the single trial.

DR. MOORE: Thank you. Dr. Masur?

DR. MASUR: Well, it's gratifying to see that all of us here have the same goal, that the federal agencies, the academic partners and industry would all like to get a drug approved for VABP. So I think at least we're much further along than we were a decade or two ago. Doing one trial seems to be a monumental task, so doing more than one trial I would agree is unrealistic.

It's interesting that while the focus of the trial may be confounded by comorbidities, I'm more
concerned that a HABP trial is confounded by lack of knowledge about what the etiology is. So that knowing what our target organism is, is important.

So I guess I would err on the side of going to VABP, because I think we also have some other important parameters there. Time on the ventilator, time in the ICU, time in the hospital are all important parameters. And yesterday we were talking about how you feel and, in a way, getting off the ventilator and out of the ICU is some indicator of how you feel. So I would go with VABP.

Now, what the supporting data would be I think really depends on what kind of drug we're looking at, because if we're looking at a drug for highly resistant Gram-negatives, community-acquired pneumonia is not going to be the right comparator, and we're going to have to go with an abdominal or a sepsis or some other indicator.

So I think that remains to be seen. But given the fact that I think we all recognize that the world isn't perfect, I guess if we had one convincing trial on a pulmonary infection and a supportive trial
showing that the drug had antimicrobial activity, and there's no plausible reason to think it wouldn't work with pneumonia, I guess I would accept any other kind of clinical trial, again, looking for all the supportive data that we can to confirm the pulmonary indication.

DR. MOORE: Thank you. Dr. Wiedermann?

DR. WIEDEMANN: I also would be pretty strongly supportive of the single VABP trial, and I'll just mention one thing that no one has brought up yet. I'm in general agreement with what most people have said. But this morning, I think Dr. Craven had made an analogy between ventilator-associated infections and UTI, and I see why he's doing that with upper versus lower infections. But I think that's the one type of supportive evidence we don't want for these patients, because the biology of the infection and the pharmacology involved are so different that I think we need to stay away from that. And as Henry said, maybe if we're talking about resistant Gram-negatives, go a little bit different route.
DR. MOORE: Thank you. Dr. Calhoun?

DR. CALHOUN: I'm afraid I'm going to have to pour a little sand in this well oiled machine. I'm not sure that I think that a single trial is a good idea, with the caveat that a large single study that's adequately powered, perhaps 90 percent powered, and perhaps even powered well enough that important subgroup analyses could be done, whether you call that one big study or you call it two smaller studies, might just be a matter of logistics.

   But I do think that there's an important point that we haven't talked about, which is that replication is an important piece of science. And particularly when we're talking about a non-inferiority -- and Dr. Fleming, in particular, but others have talked about all of the biases that are going to factor in here, they're more important today than they were yesterday, and all of these biases bias toward the null; that is, to make a non-inferiority finding more likely.

   I guess for that reason, I'd like to see replication. I'd like to see two independent trials,
even if they were a little smaller and a little more focused.

There's another aspect here with respect to the focus of the trial, and I agree with Dr. Masur on this. I think if you're going to do a single indication and then spread the indication, that VABP is the target, because you'll have better microbiologic understanding of what the pneumonia is about vis-a-vis supportive evidence, understanding that the microbiology can be quite different depending on organ system. And so Gram-negatives may well only be able to studied in complicated abdominal infections.

It still troubles me that we might take a skin structure infection study and use that in support of a pneumonia study. The lung is really quite different. The delivery of the antibiotic to the lung is entirely dependent on the bronchial and the pulmonary vasculature that can be really quite abnormal in the various disease states that we deal with. And we already have the daptomycin data to show that, unexpectedly, it didn't work in the lung
where we expected it to work. So I'd be pretty uncomfortable in looking at a skin structure infection study as being profoundly supportive for pneumonia.

DR. MOORE: Thank you. Dr. Shyr?

DR. SHYR: As I said yesterday, again, we are trying to balance the ideal design versus feasibility, that this is even harder. What all of us know, as trained statisticians, we know two studies are better, but, again, this non-inferiority trial, the results from the first study may significantly affect the second study's recruitment.

On the other hand, if you run a single big trial, the risk for the trial really is high. We know that you only have one study there. Combine all this together, but I have to support -- if I have to pick, I still think one single trial is -- but a key issue here is a well controlled single trial is acceptable in this case.

Again, we need to do good stratification. We want to see within each strata the difference -- VABP or HABP to have a reasonable
outcome. So at the end, I do support a single study, but the key word is a well-controlled single study.

DR. MOORE: Thank you.

Dr. Rex, did you have something to say?

DR. REX: I do. Thanks. So, first, I believe that a single trial is absolutely adequate. There is strong literature on the concept of a single clinical trial with confirmatory evidence that I would encourage my colleagues on the advisory committee to read, a number of papers published in the early 2000s. The intent that such an approach is acceptable is so strong that it was written into law by the Congress as part of the 1997 FDAMA legislation. Supplemental data can come from another indication. They can come from both phase 2 dose justification work or the like.

The FDA has included as part of the briefing material the FDA May 1998 guidance for industry. It's the document with the flashy red stripe on the cover. I would encourage you to read for its excellent analyses.

A single clinical trial certainly helps
feasibility, and the math is obvious why that would be valuable. And my clinical experience suggests that HABP and VABP are sufficiently similar that I see no reason to separate them. If you would like data on both, your best chance is going to be as part of the single clinical trial.

As noted in the early presentations, an earlier presentation, we do merge closely related variants already, like appendicitis and colonic perforation as part of complicated intra-ab. They're not quite the same, but they're close enough.

Having said that, I have to point at a question that's embedded in questions 1, 2 and 3 that nobody has commented on, and that's the choice of endpoint. All of these questions we're being asked to opine upon some trial designs that are based on 28-day, all-cause mortality as the endpoint. And I've already heard some questions that point at the idea that maybe folks are not a hundred percent comfortable with that. You heard presentations this morning suggesting that that endpoint, while attractive for its simplicity, is problematic as the
I have to agree you can use it. There's nothing that says you can't use. You should be able to use mortality as an endpoint. But is it the only endpoint that developers in the future are going to be permitted to use? And that's the question that I would encourage the advisory committee to debate a little bit.

It's an option that locks us into -- sorry. As the sole option, it locks us into a difficult box. In particular, what do we do in the future when mortality falls due to better supportive care? The trial sizes will rapidly become unachievable. What if future changes in the rules for clinical trial enrollment make it even more difficult to enroll the most severely ill patients? We actually face this situation already in CABP, where we can't actually -- we could use mortality in CABP, but the reason we can't hit the 15 percent mortality in the CABP patients is you can't enroll them. They're too sick. You can't enroll them.

Then, finally, what do we do with all the
critiques we've heard about mortality, just the other
issues with it? So I think we need to debate this.
And the alternative endpoint that's been brought up
is one that includes critical measures of how a
patient functions during the early days of therapy,
oxygenation, blood pressure and the like.

I think that such an endpoint should be
debated. It has the advantages of incorporating
elements that make intuitive sense to physicians and
that have value to patients. The endpoint also has
the value of having a failure rate that's a little
bigger than the mortality rate, because I would
assume you'd have to also live in addition to getting
better -- those two things do seem to go
together -- which has enabled us to stay a little
closer to the 20 percent failure rate that is so
important for reasonable trial designs.

An earlier response measures is also
intuitively similar to the approach taken by the FNIH
for skin and CABP, where, as we heard yesterday, it's
important to go where the treatment effect is the
largest, and that's early on in the course of
therapy. So if it's 28 days out, it's a long time to wait.

Now, there's a critique that's going to be raised, and let me raise it right now, and it has three pieces. The first is this is based on a biomarker or a collection of biomarkers, so all that stuff, those clinical things that we look at are biomarkers. Those biomarkers are ill defined or, rather, the way we decide about them is ill defined, and we need to derive a non-inferiority margin. And let me take those one, two, three.

First, it's a biomarker. There's nothing wrong with it being a biomarker. We simply need to know that it links to an outcome of interest. You heard a lot yesterday about the FNIH and community-acquired pneumonia. What you didn't hear about was the FNIH spent a lot of time looking at skin infections, and in skin infections, the document submitted to the FDA by the same group concluded that a biomarker, the amount of erythema around the site of infection, was a perfectly valid endpoint for skin infections, a biomarker or endpoint for skin
infections right there in the FNIH document.

Do we have perfect validation of the biomarker outcome linkage? No. But does it make good biologic sense? Does it fit the years of experience? Does it make good intuitive sense? Absolutely.

The FNIH concluded it could be used because it was a tractable path forward that tied a lot of things together. I think we have the same situation here. Yesterday, Dr. Calhoun foreshadowed the importance of oxygenation-related parameters as biomarkers that are intimately connected to how we function -- how I breathe is a lot about how I function -- and I see no problem with connecting these dots.

Second, there is a concern that the endpoint is ill defined because it contains a subjective component. A physician must look at the patient and decide whether the patient is improving. Unlike mortality, which anybody can count, this endpoint necessarily involves a thought on the part of the treating physicians. Thus, there is a concern that
clinical decision-making is so subjective as to be unreliable.

Here I have to differ and differ strongly. Those of us who have extensive ICU experience know that it is possible to manipulate oxygenation status by twiddling the ventilator settings. It's also possible to manipulate fever by giving antipyretics. And for those who favor a 28-day mortality, I'll note in passing that I can modify even that. I can get you to 29 days, if you really want me to.

But the critical point that is overlooked, but alluded to in my little joke there is that it's only possible to manipulate these variables up to a point. Yes, I can cram more oxygen into your blood by pushing up the pressure on the ventilator, the pressure with which it pumps into your lungs, up to a point. But at some point, you have to get off the vent, and I can't cheat then. I'd have to gradually withdraw the ventilator support, and then you have to do the work on your own.

This, the progression toward coming off the vent, this is a solid measurable event that is
surprisingly consistent across patients, physicians and ICUs. It's so consistent that we actually write it down in our weaning protocols. It's a known plan.

That's the basis of the clinical endpoint used in modern research in this area. The subjective manipulable component of this response is really much more objective than has been appreciated, and I think we need to say that and say it clearly. It's not as subjective as you think.

So, again, I have no problem connecting the dots.

Finally, if you're going to do this, where are you going to get a margin? So you guys, I hope, have appreciated by now we have to be able to derive a margin based on some data, not just something we make up. Here, again, we have more than is recognized. Recent work from the field of pharmacometrics has shown that clinical outcome and HABP/VABP based on these ideas correlates very tightly with pharmacodynamic predictions of response.

As presented in several venues over the past year, as an example, Paul Ambrose has shown that the
observed AUC MIC in patients with HABP predicts response. This makes perfect sense. Those who achieve a low exposure, those who have a high MIC isolate, or those with both problems should do worse. This is the basis of all of infectious diseases. The pharmacological effect of antibiotics is their effect on the bacterium, and we know that adequate exposure is required for this.

For HABP, Ambrose's data suggest that substantial M1 for a clinical endpoint of the type I've just been describing, not just mortality, clinical endpoint -- according to him, the best estimate of this clinical endpoint size is 41 to 67 percent with a lower bound of 20 to 30 percent. For the clinicians at the table, this is proof that your intuitive sense that antibiotics have a huge treatment effect is correct. Correct antibiotics at a good exposure really, really make a difference, and these estimates are roughly similar in size to the mortality size estimate. It makes good sense. So you have to survive and improve.

You can critique the pharmacometric
endpoint, and please see section 3.2 of the FNIH CABP
document from yesterday if you would like a detailed
summary that we wrote down very carefully. These
critiques boil down to a concern that there's an
unmeasured covariate that is driving the observed
correlation; that is, there's something we don't
measure, being left-handed, glucose transport,
polymorphism, something that explains the observed
correlation.

It's a theoretical concern, but the specific
case for infectious diseases is associated with an
overwhelming set of data. The pharmacometric
approach works across drugs, drug classes,
indications, modes of drug excretion, modes of drug
administration, IVPO, patient age, severity of
illness, and more.

The theoretical unmeasured covariate would
also have to simultaneously modify both the observed
MIC and the observed drug exposure in a symmetrical
fashion so that their ratio is maintained. Quite
frankly, I can't imagine a covariate that could
simultaneously do all these things.
My former and, I should say, intellectually, current and future boss and mentor, Jack Bennett, has just offered a critique of MICs, that while is true, you can manipulate MICs. I have to point out that when you use a standard method for MICs, they are reproducible in terms of their relative values. And when you change methods, the isolates retain the same rank order. So the isolate with the highest MIC will always be the isolate with the highest MIC in a new method. So as long as rank order is maintained, the pharmacodynamic stuff works just fine.

So I can connect the dots. And I have to point out, pharmacometrics is extraordinarily interesting because it offers proof of efficacy, proof of superiority over no exposure directly from modern data using modern supportive care and modern endpoints. That's its huge power.

So I'm going to stop my monologue here; sorry about that. But this for me is an area where we need more than one solution, and that's my theme for today. Don't lock us into a single answer that we regret and doesn't allow us to make progress going
forward. Mortality can be used, but I think serious
effort needs to be put into the question of is there
something else that's equally valuable, though it may
cost -- we may have to change the shape of our brains
a bit. Thanks.

DR. MOORE: Thank you, Dr. Rex.

Okay. So Dr. Rex has opened the door. He
alluded to answering the other questions in the
discussion, as well.

So let me go back to Dr. Reller on this end
of the table. We'll cover briefly the second
question regarding the non-inferiority margin at
10 percent.

DR. RELLER: It's always a pleasure to be
the first to have a go at these.

[Laughter.]

DR. MOORE: I promise I'll change it up the
next time.

DR. RELLER: I don't mind at all. It has
been my observation on committees of different kinds
over time that a consensus seems to emerge the
further one is down the asking order.
[Laughter.]

DR. RELLER: Now, question 2. Please discuss if a non-inferiority margin of 10 -- I have learned a lot and have greatly appreciated the statistical discussion today, more than in any past meeting. And it seems to me that the 10 percent is so linked with an assumption of 20 percent mortality to have the sense of being relatively confident that we're not missing -- that is, if we're going to use non-inferiority, that I am very -- I'm enamored of the odds ratio to get around this that would enable some consistency, as I understand it, with changes in mortality rate, be they changes owing to improved intensive care or improved efficacy of antimicrobial agents.

So that’s all I have to say about question 2.

DR. MOORE: Thank you. You know I pick you so we can set the tone for the rest of the consensus.

[Laughter.]

DR. MOORE: Dr. Fleming?

DR. FLEMING: In prefacing my comment to
question 2, it does in fact explicitly indicate, I believe, that we're thinking in terms of mortality as the endpoint. So prior to answering question number 2, I'd like to respond to Dr. Rex's comments that he's just made.

  It's certainly true that we need to look at other measures beyond mortality. To argue that we should look at measures that are composite endpoints that may not reflect mortality effects when mortality is such a profoundly impacted and important endpoint, just from a clinical relevance, I have great concerns with.

  I think the measure that he was talking about was a measure that was presented in one presentation. I think all the presentations that I recollect today recognized the importance of mortality and that we need to assess effects on morality, but we may, in fact, need to look at other measures in a supplementary way. And I'll defer comments. I endorse that perspective. I'll respond to that more when we get to question number 3.

  There was the one presentation, though, that
talked about a composite endpoint that was 28-day survival, physiological improvement, and no change in antibiotics, and it was called mortality-plus. That's a skillful term. I guess I could call in heart failure, heart failure hospitalization-free survival as mortality-plus, if that makes it sound more mortality-like, even though that would be very misleading.

Its interpretation is, in fact, less clear because it is a composite. It is a composite of mortality, which the patients most care about, and a physiologic measure, which is an indirect measure. It is a direct measure of biologic activity. It is not a direct measure of function in the function, feel, survive context of how is it affecting how a patient can function and carry out normal activities, and it's not validated as a surrogate endpoint.

So there would be serious problems with this endpoint if we went back a week to the October 27th, 2011 FDA clinical outcome assessment workshop, talking about the importance that measures that we choose are well defined and reliable, properly
validated for content validity, and either direct
measures of functions, feels, survives or validated
surrogates for those.

Dr. Rex correctly anticipated a lot of the
key issues of concern. The margin, there has been no
data presented that would -- even if we put aside the
important consideration that this is not directly a
mortality endpoint and isn't fully validated or well
defined and reliable, there are issues around the
fact that there is no evidence-based justification
for a margin, as FDA has indicated.

The argument that we could use physiological
data, which is certainly very good for hypothesis
generation, but the argument that we can treat a
number of people and look at their different
physiological response and see that that
physiological response is correlated with a clinical
outcome, and conclude that the induction of that
physiological response was the sole causal factor to
lead to the difference in the clinical outcome is
certainly completely untenable, because the fact that
somebody has a different physiological response than
someone else, obviously, is an evidence that they
have a different immune system or some aspect that's
different. And so, in fact, it's very likely that
the difference that you see in outcome is completely
confounded by what is causally induced by the
treatment and the inherent differences in those
people who have a better physiologic response than
others.

There's no basis and, in fact, I think the
data that was used that was discussed in FNIH -- and
as Dr. Rex correctly pointed out, in section 3.2,
there were clear arguments put forward about the
vulnerability of this type of evidence looked at
beyond just hypothesis generating, I think was the
tigecycline data. And the tigecycline data would be
a poor choice to use, because, in fact, there's
evidence that it's not picking up excess effects on
mortality.

So clinical relevance is also an important
consideration. With a composite endpoint like this,
you might have -- you could readily have, in an
active control, 15 percent who die, and in the
experimental arm, 25 percent who die. That would be a completely unacceptable scenario. But among those people who don't die, 15 percent of the 90 who don't die on the active control could have shifted their antibiotics or not had a full physiologic response, and only five of the experimental may have. The end result is you have non-inferiority on this composite endpoint of 30 percent failures on both arms, even though you have a 67 percent relative increase in mortality with the experimental arm.

The concept that a composite is survival-plus is very misleading. It's moving away from survival to a physiologic measure and a change in antibiotics. I'd ask, as a patient, what's your goal in this clinical setting. Is your goal to have a change in a physiologic measure; is your goal to prevent the augmentation with another antibiotic; or is your goal to prevent survival?

Antibiotics are enormously effective in this setting. The goal here is to not just offer patients a choice, but an informed choice, meaning that if we're going to give you an alternative to what's an
established effective agent, we need to be confident
that the most important thing that this agent is
doing, the standard of care is doing, isn't lost;
i.e., that you're not losing survival.

So I fully endorse -- and I'll talk at the
end in the next question -- that, yes, we want to
look at things beyond survival, but we surely do not
want to remove survival as an integral component of
what we need to assure we're not losing in this
setting.

So with that as background, the question.

Non-inferiority margin of 10 percent, is that
acceptable when the mortality rate is less than
10 percent? Does the odds ratio approach let us move
forward?

There is, in fact, an evidence-based margin
that's justified of 10 percent if the active control
background rate is at least 20 percent. If, in fact,
though, the active control background rate is less
than 20 percent, particularly discernibly less than
20 percent, there isn't an evidence-based
justification for a 10 percent absolute risk
difference margin. But the good news is there's a way forward. There is, in fact, an evidence-based justification for a floating margin that's defined, based on an odds ratio, of 1.7. So, in fact, we can proceed. We don't have to know the exact background rate that you're going to have on the active control arm, and we can, in fact, define a non-inferiority margin using an odds ratio-based formulation for what that margin would be.

So it gives us, in essence, a robust approach to carrying out these trials without having to have complete certainty upfront as to what the active control mortality rate will be. It's a very commonly applied approach in other disease areas. In fact, in the FDA guidance document on non-inferiority trial methods, they prefer a hazard ratio, odds ratio approach for its robustness in defining margins.

This issue may not be that critically important. If we can achieve something close to a 20 percent mortality, then a 10 percent margin is in place. And, in fact, if we are not too exclusive in eligibility -- there was an example given in the
doripenem trial where we were getting a lower mortality rate, where it was a pretty exclusive strategy in place there for who we included. We didn't include -- we excluded unstable patients, we excluded patients that had immediate life-threatening conditions. Well, that could exclude a lot of people. Furthermore, if a 28-day is used, obviously, that also gets us closer to 20 percent.

So this issue probably isn't going to be too critical if we're able to enroll -- and the evidence I've seen suggests that we can by being inclusive in our eligibility and by having 28-day mortality for getting 20 percent. But if we're less, we're fine, because an odds ratio approach does give us an evidence-based justification.

One last point. There are clinical considerations that we have to think about, as well, in terms of what that margin could be. There was still some discussion, although my sense of the discussion has been the 10 percent margin is as large as people have been willing to go. But if you said I'm going to try a 15 percent margin, when there's a
background 15 percent mortality rate, if you had 400
patients per arm, that trial would be positive if you
observed a 15 percent against 21 percent mortality.
If the experimental had a 40 percent higher mortality
that would be statistically significantly higher, you
would meet that 15 percent margin.

So M2 clinical considerations come into
place, as well, and would argue, I would think,
strongly against margins for mortality that would be
greater than 10 percent.

DR. MOORE: Thank you. Dr. Fratzke?

DR. FRATZKE: How do you follow that?

[Laughter.]

DR. FRATZKE: I got the highest learning
curve on the table here, and so I'm going to leave
the answer to this question to the people in the
know.

DR. MOORE: Thank you. Dr. Goetz?

DR. GOETZ: Well, I'll try to follow. I
accept the points about the odds ratio being
preferable and more stable, especially as mortality
rates may go down, as we hope they do for our
patients, as supportive care becomes all the better.

Very clearly, though, I think there are also advantages to making sure that we do enroll patients in the severe end of the spectrum of severity of disease so that we're using the historical data to the best of our abilities. In that regard, we'll get to discussions about prior antibiotic use and their role as we go forward.

Again, we'll touch on these issues several times, but I think Dr. Rex's point about being able to keep a patient alive to day 29 is well stated, and I would regard that if reliance on pressers and the reliance on mechanical support is the way that -- what it means to be alive is fundamentally changed by application of many of these technologies, and the path forward to using them I recognize is complex, but I think it's something that we really need to consider.

As I muse upon Dr. Rex's challenge to come up with a metric that will work for the next 10 years, I don't know that we can get there today. I'm reminded of the sign in my auto mechanic's shop,
"Fast, cheap, high quality service. Choose any two."
I'll stop right there.

[Laughter.]

DR. MOORE: Thank you. Dr. Neely?

DR. NEELY: Oh, boy, here we go. First of all, Dr. Bennett, I accept your apology. Thank you.

[Laughter.]

DR. NEELY: So the pharmacometrics gauntlet has been thrown down, so, of course, I need to try to pick it up. And I recognize that I am coming into a discussion that's been going on for 10 years, and more intensely perhaps in the last four or five years.

First of all, in specific response to your point, similar to what Dr. Rex said, when an MIC is done under standard conditions, it's not going to vary as much, maybe one or two tubes, that's fine, as long as it's relatively the same. And pharmacometrics is a stochastic discipline, so we're always dealing with probabilities and uncertainty anyway.

I think it would be hard to really ignore
pharmacometrics. In older terminology, you could even think of it a PK/PD associations, and the point about association as opposed to causality is well taken, but I'll address that in a minute.

But there's so much evidence that supports at least the strength of the association, again, as Dr. Rex mentioned, across animal models. There's also human data, there's in vitro data, numerous drugs, numerous indications. But I think maybe just -- I agree with pretty much everything that Dr. Rex said. But let me add to that, because in response to a point that you made, Dr. Fleming, about that there could be a physiologic change that is sort of that unmeasured covariate that is causing people who have worse outcomes to have lower concentrations of antibiotics, as well.

First of all, we generally know the factors that affect concentrations or pharmacokinetics of antibiotics. Usually it has things to do with renal function, liver function, perhaps the volume of distribution, which can be all modeled and accounted for often. And so we nonetheless see different
exposures in these patients who don't necessarily have changes in those covariates that we're talking about.

What really, I think, is compelling, though, is that there are concentration control studies out there where we actually do control the concentrations, where we're not just allowing the concentrations to be randomly different between patients, and we see differences in outcome. Courtney Fletcher did studies with HIV drugs, and he controlled the concentrations of zidovudine, lamivudine and in Denavir and showed quite a statistically significant difference in virologic outcome for HIV. So here is where it's not just a random concentration, it's a controlled concentration and we're getting a different outcome.

Nathalie Bleyzac did concentration control studies for busulfan and the incidence of VOD and showed, again, a statistically significant decrease in the incidence of VOD in patients who were concentration control with busulfan.

There have been studies with mycophenolate,
several studies with mycophenolate, tacrolimus, as well. And then another one specifically in the area of antimicrobials was the study by Lent-Evers, and they looked at aminoglycosides, and they did concentration control therapy for aminoglycosides and showed, again, a statistically significant improvement in mortality and, actually, a statistically significant decrease in cost, even factoring in the expertise to do this concentration control.

So we have prospective evidence that by controlling the concentrations, we can improve outcomes. So I think that really gets away from that issue of some unmeasured covariate, which, again, like Dr. Rex brought up, I'm a little hard-pressed to figure out what kind of unmeasured covariate could be so broadly applicable across all of these circumstances. And I think, again, the prospective nature of what I've described makes that less of a concern.

Having said all that, really, to me, the only -- not the only, but one of the reasons that
we're locked into this mortality endpoint is that, as was presented in the documents that the FDA gave us to review, they couldn't find enough historical evidence to come up with any other endpoint besides mortality.

Well, if we accept the use of pharmacometrics, then we do have other endpoints. And it strikes me that we spent a lot of time yesterday for community-acquired pneumonia accepting the fact that we could have a short-term outcome as the primary outcome of the studies; it was not mortality. And yet here, we're sort of saying all we have is mortality, and we can't have a short-term outcome as the primary outcome, and I'm not sure why not. If we can define an effect size using pharmacometrics from modern trial data, then I think we can have even a primary outcome that was a short-term and have the mortality as a secondary.

I really echo some of the concerns that have been made before about mortality, a 28-day mortality for, say, maybe a two-week treatment period. You could easily have somebody who has an MI after their
treatment for ventilator-acquired pneumonia, and are
we going to blame that on antibiotic failure? That
makes no sense at all.

    So I would really like to, in regard to
question 2, question the whole assumption that we are
locked into a mortality endpoint. I think it's an
important endpoint, but just like the discussion
yesterday, I think it can be a secondary endpoint and
have a primary endpoint be the actual response of the
pneumonia, the ventilator-associated pneumonia to the
antibiotic therapy. But, obviously, we can't get
there unless you accept pharmacometrics as a way to
get that M1 since we can't get it from historical
data.

    Now let me just quickly look at my little
notes here and see if I had anything else to -- oh,
yes, one other point. CLSI has certainly embraced
pharmacometrics. Think about how many breakpoints
have been revised on the basis of pharmacometric
associations between exposure and MICs. So, again,
there's probably more evidence to support
pharmacometrics across a wide range of studies,
indications, drugs than just about anything in infectious diseases.

DR. MOORE: Thank you. Dr. Follmann?

DR. FOLLMANN: Let me say a little about pharmacometrics. I didn't really know what it was until like three or four months ago when it came out of the FNIH, and I found it kind of intellectually fascinating, actually. But personally, I think the comments that Tom made about being circumspect about its use sort of holds resonance with me.

It's not like I want to quit thinking about it or discard it completely, but I still have these reservations, and I would just put it -- the pharmacokinetic parameters, I understand, involves both an AUC and an MIC, and the analysis they like to do is to pretend as if on the effective concentration, that ratio is randomly assigned to people; that I randomly pick a person, and you get a 4, you get a 3, you get a 1, et cetera.

In fact, that's not what happens. What happens is that you have both the AUC and the MIC involved in this. So we have to imagine that we're
randomly throwing pathogens at people, so I'll randomly give you something and give you something else. And then we also have to randomly -- we have to assume that people sort of randomly are able to metabolize the drug in a way that's unrelated to everything else about them that might affect mortality.

So if you buy those two things, then I agree, you sort of have randomization level inference based on pharmacometric type data, but you have to sort of assume those two things, that both act in sort of a random fashion. And I'm not here really today to say whether that's so or not, what the evidence is or not, but, to me, that's the fundamental concern about pharmacometrics, and it might be interesting to have a big discussion about that sometime, but not right now.

So getting back to question 2, I think we've discussed this pretty well, and I think it's pretty clear. Ralph has pointed out there's been trials that he's been involved in, and I have been involved in, too, where a fixed margin was chosen based on an
assumed underlying event rate that was quite
different from what actually happened, and then the
trial was kind of a disaster or a problem.

So I think it's absolutely necessary to try
and get away from the 10 percent fixed margin if
you're not super sure you'll have 80 percent
mortality, more or less. And from what we've heard
over the last day, we expect the mortality rate is
likely to be less than 20 percent. So I think we're
obliged to use an odds ratio or maybe a risk ratio
metric that can be calibrated to the different event
rates that we would have.

I thought it was gratifying that Tom pointed
out the paper that he and John wrote showed that
there was this margin of odds ratio, 1.7, for
different underlying mortality rates. It wasn't the
exact same setting, but it was similar enough that it
makes me comfortable to endorse, I guess, the odds
ratio metric and certainly get away from the fixed
10 percent.

DR. MOORE: All right. Thanks. This is
Dr. Moore. I don't really have many additional
comments or certainly no more insightful comments to
make about this particular entity. It seems to me
the odds ratio, as Dr. Fleming pointed out, would be
the best metric to use for situations where you start
off with an assumption of a 20 percent mortality, but
then come to find out that it's going to be less than
that in the conduct of the trial, which is possible.

Even though it may lead to the enrollment of
more patients, it seems like you've got that
statistical tool to help you make sure that the
differences between the drugs, the active comparator
and the study drug, are identified.

Dr. Chatterjee?

DR. CHATTERJEE: I'd also like to concur
with some of the comments that have been made with
regard to questions 2 and 3. I think these sort of
go together, in my mind.

Thankfully, it appears that mortality is a
moving target and it's moving in the right direction
for these two conditions, whether it be due to
improvements in critical care or other measures that
have been put in place. But because of that, I think
that this fixed measure of a 10 percent margin statistically does not make sense. It's going to mess it up if you get into the context of a clinical trial.

So although easy to measure, the all-cause mortality endpoint on which the non-inferiority margin is pegged is fraught with difficulty. So I would concur with Dr. Fleming's analysis that the odds ratio, which is more stable with the changes in the mortality, should be the metric that we use, and that although he supported the all-cause mortality endpoint, I would suggest that some way of measuring endpoints, composite endpoints that are more clinically relevant closer to the end of therapy, would be more useful.

DR. MOORE: Thank you. Ms. Young?

MS. YOUNG: Yes. For the reasons that have been mentioned, I would support the odds ratio as long as it reflects a non-inferiority margin of 10 percent with an active control mortality rate less than 20 percent. So you're trying to equate that effect. And so if there's a way to do that, that's
statistically more valid, that's great.

DR. MOORE: Thank you. Dr. Weinstein?

DR. WEINSTEIN: I have nothing to add to Dr. Chatterjee's comments.

DR. MOORE: Thank you. Dr. Cappelletty?

DR. CAPPELLETTY: Not being a statistician, I really do defer on some of this. Again, the arguments made were compelling for the odds ratio. One of the things that intrigued me earlier was what do you do with an odds ratio versus the ease of interpreting a relative risk. So maybe for the average clinician, if some sort of interpretation could be made as to what that odds ratio was relating over to, would probably be good.

DR. MOORE: Thank you. Dr. D'Agostino?

DR. D'AGOSTINO: I hope you don't hold it against me if my answer isn't brief. I'm going to have sympathy with my students who come to me and say I really don't know how to answer the question you asked, but I do have an answer to another question. [Laughter.]

DR. D'AGOSTINO: As far as the question
that's being asked here, the 10 percent is a trap and
for the reasons that have been mentioned. You find
quite often when you design a trial you start off
with a preposition, an assumption that you're going
to have, say, a 20 percent mortality rate. It
doesn't materialize. If you have the 10 percent
margin, you may end up in a trial that's very hard to
interpret. If you have the odds ratio or the
relative risk, then you can move around, and the data
can still be interpretable. So I would definitely go
for the odds ratio.

DR. MOORE: Thank you. That was actually
quite brief.

Dr. Bennett?

DR. BENNETT: Dr. Masur and I work in a
hospital, which justifies its existence by doing
clinical research. So we collect a lot of data, and
it's all being collected by study nurses, not
doctors.

The reason is the doctors don't collect it
anywhere nearly as reliably or accurately as the
study nurses. So there's an advantage of having them
do it. But one of the disadvantages is don't ever ask them to actually track down a patient, because the patient is not in their room, if it's a hospitalized patient. They're down in x-ray, or they went to the cafeteria, or the library, or they're having a procedure. If it was a clinic patient, "Oh, well, we sent him off for a neurology consult, so they're not here." So they like to collect data based upon the chart or word of mouth. And so I like endpoints that are very easy to tally, and morbidity is difficult, but mortality is absolute. So the patient is dead. You may not know why, but you certainly know what. And so I'm in favor of, for several reasons, mortality.

Now, I've never liked absolute differences for an endpoint of a study. It never made any sense to me, and this has been widely discussed here. But my problem about odds ratios, as Diane Cappelletty has already referred to, I don't know what it really means. I can calculate it, but I have no intuitive understanding of what a 1.71 odds ratio means, and I doubt I could explain it to the house staff.
However, relative risk makes a lot of sense to me. So I like mortality 10 percent, but adjusted for relative risk.

DR. MOORE: Thank you. Dr. Masur?

DR. MASUR: Sometimes federal agencies are accused of speaking with one voice, so I'd like to just try to speak with a different voice from Dr. Bennett, and I probably will be unemployed next week.

[Laughter.]

DR. MASUR: But while I won't comment on the statistical issue, I think that we had a lot of momentum until recently on looking at things other than mortality, because I think particularly when we look at VABP, as a number of people have indicated, there's so much comorbidity, there are many reasons why people are alive or not alive.

I think when we were talking about physiologic parameters yesterday, Mike made the point that with community-acquired pneumonia, you can change blood pressure, temperature, oxygenation all sorts of ways, if you'd like to so you can get the
result you'd like.

   To me, the simple issues are what John said before. I mean, I agree with Jack that you can tell whether the patient is alive or dead. In our hospital, at least, you can tell whether they're in or out of the ICU, and you can tell whether they're in or out of the hospital.

   Now, whether or not they are sent out of the ICU to die, I think there are probably things one ought to look at, how much respiratory support they're getting, is it more or less than when they came into the ICU. But I hope we have some momentum to consider something other than mortality for a primary endpoint, because I think that, to me, is inescapable for the population we're likely to be looking at. And I'll leave it there and start packing up my office when I get back.

   [Laughter.]

   DR. MOORE: Thanks. Dr. Wiedermann?

   DR. WIEDERMANN: First of all, just an aside on the odds ratio being understandable or not, if more clinicians bet on horses, this wouldn't be an
DR. WIEDERMANN: If you talk to someone who bets the horses, we'd be poor, but you'd get it. And I think that can be explained with whoever is writing the article or the journal editor to make it clear.

I think, clearly, the risk difference of 10 percent is a trap and certainly favor the odds ratio route. But part of my question to Dr. Komo this morning, that I don't think I ever got answered, was the fact that as control mortality falls, the sample size requirements rise asymptotically almost. So I think the odds ratio solution is a trap, also, and we just have to be prepared to deal with that if it happens in some of the early studies.

Then I want to rebut a little bit what Dr. Rex said. I don't think it's advisable to come up with a 10-year solution for how these trials are run next month. I would refer more back to the IDSA recommendations from that 2010 supplement in CID. And I won't go through it, but in the executive summary, the end of item 2, where we choose a
reasonably feasible trial design now, but then work very vigorously to develop these other endpoints that could be used as primary endpoints in future studies rather than just using all-cause mortality.

If Dr. Neely or others have pharmacometric cool data in the meantime, that's the time to develop it. And then the agency needs to be nimble and be able to incorporate some of these new evidence into revised guidelines.

DR. MOORE: Thank you. Dr. Calhoun?

DR. CALHOUN: So with the caveat that's been expressed that all-cause mortality may not be the best primary outcome, I think there really are some good reasons to try to look at shorter-term outcomes that are based in physiology from which we can generate objective non-inferiority margins. Those are all good ideas. I do think that having the mortality as one of the anchor points is a good thing and, for reasons stated, probably needs to be expressed in terms of a ratio, either risk or odds.

DR. MOORE: Thank you. Dr. Shyr?

DR. SHYR: As you can guess, as a trained
biostatistician, we definitely vote for odds ratio.
I'm actually a little bit surprised. I think a lot
of diseases, especially in cancer, every day we talk
about odds ratio. I'm just surprised that in this
room, odds ratio comes as a new. But I can tell you,
from a statistician's point of view, definitely
that's the way I think we should we go.

DR. MOORE: Thank you. Dr. Rex?

DR. REX: Thanks. First, a minor comment
clarifying my thinking around the suggestion
regarding an endpoint that includes 28-day survival
and some measure of early clinical response.

Tom has correctly taken me to task for not
having made it clear that if one is going to use that
composite endpoint, implicit in that is the
requirement that the mortality component will need to
be similar in the two arms. If there's a dramatic
difference between the two arms, we're all going to
look at that and say and I don't know what that means
and we're not going to like it.

So if I failed to make that clear, I
apologize. It's the kind of thing that we've
discussed so many times, you kind of forget the prior reference.

There's a risk there to the sponsor, as small differences in mortality occurring by chance could take on a magnified significance. We've all become very sensitized to that. And I think the sponsor would need to consider that and ensure that the risk of that is low enough for comfort, and that's going to mean pushing to enroll people with reasonably high mortalities. It makes the trial more robust. It's closer to the basis of our non-inferiority margin support data. And if you're at the very low end of the mortality curve in this disease, it's going to look a little suspect in terms of the quality of your patients and cases, unless, of course, the overall trend in modern care is such that mortality rates are really driven down. And when that begins to happen, if it begins to happen, and there are new therapies for sepsis coming, there are new objective therapies coming, mortality rates in HABP/VABP might really fall over the next 10 years due to things beyond antibiotics. So we actually
really do need to think about that.

In terms of a specific margin, I agree with Dr. Wiedermann that both odds ratio and absolute difference have a trap built into them. I don't have a best answer to this, to how you handle the fluctuation. Hopefully, it won't fluctuate in the course of an individual trial.

What I don't know is whether there's a way that we can kind of have our -- you know, sort of pick the best of both worlds or do a trial where you're monitoring in real time the overall event rate and determining when you've crossed a given threshold. I don't know whether that's possible or not.

But there are two other themes that we've not talked enough about. One is the -- I just heard the comment about I can't solve all the problems now, can't do a 10-year timeline now. Guys, you've got to deal with 10 years from now today because that's the cycle time for antibiotic development.

The drug developers who will be bringing you your drug in 10 years are listening to this
conversation today and deciding whether or not to play. That's why you have to solve the problem. You can't leave this for an undefined, ill defined, optimistic future and then hope the drugs will occur. Drugs do not occur like turning on the faucet and dripping out. They don't.

Every drug you see coming into the clinic now got its start a decade ago in somebody's laboratory. That's how long it takes. So it really does matter that people can see 10 years into the future in terms of the approach to developing drugs.

It's astonishing to me how hard it is, how long it takes to do this. And the thing that drives that is the ability to see how it's going to be over that period of time. So even though 10 years sounds like a terribly long period of time, it's a blink of the eye for the pharmaceutical developer.

Last thing. We have spoken as if there's only one margin of interest, and that's the margin for the ITT -- sorry -- for the micro-proven ITT population. Everybody's focused on that being 10 percent.
Can we at least do the 10 percent in base 8?
That'll help a bit. And if we were dogs -- I think it's dogs that have four fingers on the front and the back paws -- it would make more sense to us.

But why haven't we thought about the clever idea that came up yesterday with CABP, where you set your ITT margin at one level and you set your micro proven ITT margin at another level? Because the people who aren't micro proven, they're still in your trial, they're still representative of the way drugs are used. Some of them still have a bacterial infection. It's not like those folks are completely irrelevant. They're just less clearly relevant, but they are part of it.

So I think there's something strong to be said about having a margin -- a margin on ITT is how it will really be used. Okay? You don't always make the diagnosis even in real life. So you're actually setting your margin, if you look at 10 percent, on the ITT to drive at the population that reflects the real world in the future.

I don't always get a culture and I don't
always make the diagnosis correctly, but that's how it's really going to be used. And you would then know that in that population, no harm, potential value, looks good. And then we focus in on the subset that's micro proven, and there we recognize the problems with microbiology, we recognize the problems with culture yield, and we back off a little bit. But we also recognize that we're not approving the drug based just on this one datum. There's either another trial in another indication, or other collections of data that said that it actually is an active antibiotic, it actually ought to work, and here's a demonstration that it did work.

Again, I point back to the themes of single clinical trials with confirmatory evidence. The confirmatory evidence helps you believe that the single clinical trial wasn't a mistake. And if the single clinical trial actually worked, albeit at a larger margin, because you have permitted a slightly smaller sample size, then you've actually picked up all the elements that you need, and you might actually get drugs developed.
So that's where I'm going with this. And I think there's a slide from PhRMA, slide 14, I think, that talks about a design of 10 percent -- the 10 percent or the odds ratio equivalent in ITT and 15 percent for the micro proven. And that actually looks like that might be doable, at least. It won't solve my pseudomonas problem, but it would solve my Gram-negative problem and my staph aureus problem, I think.

DR. MOORE: Thank you.

All right. Now, looking at how much time we have left, we have about 120 minutes before this meeting is over, we have 19, essentially 20 members of this committee. With the three questions that are left to be addressed, I'm going to have insist that everybody respond to each of the questions in two minutes or less. I'm sorry to be a dictator, but that's the only way we're going to finish on time and have everybody catch their planes.

So if you can, please be as succinct as possible, yet pack in a bunch of words, if you can. Try to convey as many of your ideas as possible.
within the two-minute period.

Dr. Reller, we're going to start -- well, actually, you know what? Let's go back this way. I'm going to give you a break. Sorry to disappoint you, Dr. Reller.

Dr. Rex, we'll start with you, and we'll go with question number 3.

DR. REX: Timing for all-cause mortality endpoint, 28 days is both as logical and as illogical as any other time point.

[Laughter.]

DR. MOORE: I think that's a record.

Dr. Shyr?

DR. SHYR: Twenty-eight days, as we know, if you want to do shorter, you do need -- actually, you need more sample size. We already talked about it's not feasible to conduct that for 28 days. I'm willing and open to any other thorough study to find M1, including the mortality and the other clinical usage information, but we need a thorough study to convince me as a statistician to determine M1/M2 echo to Dr. Fleming's echo.
So if you have mortality there, you have to have that boundary there in those combinations of the information. But the comment is we need to study thoroughly to get that information, to get M1/M2. But right now, 28-days mortality.

DR. MOORE: Thank you. Dr. Calhoun?

DR. CALHOUN: So I think the 28 days, as Dr. Shyr just mentioned, is really driven by the statistical, not by the clinical or experimental design considerations. And so I think 28 days makes as much sense as anything.

As it is possible to incorporate other data-driven outcomes that have clinical relevance, those may well be things that can be evaluated earlier, as we discussed yesterday. Those may be things that can be evaluated earlier and would add power to the study.

DR. MOORE: Thank you. Dr. Wiedermann?

DR. WIEDERMANN: I agree with Dr. Rex.

DR. MOORE: Thank you. Dr. Masur?

DR. MASUR: I agree, also.

DR. BENNETT: I agree with 28 days. Dying
in a modern hospital is a process, not just an event, and it takes time.

[Laughter.]

DR. MOORE: Thank you, Dr. Bennett.

Dr. D'Agostino?

DR. D'AGOSTINO: I think the 28 days, from what I hear, makes reasonable sense. And when people are running these trials, they'll be looking at the course up to 28 days to do time to event type analysis.

One of the things that I do want to comment on is that we had the statement yesterday, you picked the point with things of -- big differences, and that's where you do your test. That's a dangerous thing with mortality. If everybody dies by 35 days, 28 days isn't very informative. I mean, there's a reason for 28 days, that we think there's going to be something sustained after that 28 days.

DR. MOORE: Thank you. Dr. Cappelletty?

DR. CAPPELLETTY: I also agree with the 28 days, and as we get better at looking at other parameters, clinical and otherwise, they'd be nice to
incorporate once we could identify some margins.

   DR. MOORE: Thank you. Dr. Weinstein?

   DR. WEINSTEIN: I guess I'll buy into the
   28 days based on the data that were presented. But
   it's curious, because as a clinician, it would be
   fine to assess either at 14 or 21 or somewhere in
   between. So there's a paradox there, but based on
   the statistical presentation and the data presented,
   I guess 28 days is where it has to be.

   DR. MOORE: Thank you. Ms. Young?

   MS. YOUNG: Yes. I would support the
   28 days also and allow for supplemental information,
   pharmacometrics. And that would be considered a
   bonus, but, really, it wouldn't be the weight of the
   measure.

   DR. MOORE: Thank you. Dr. Chatterjee?

   DR. CHATTERJEE: This time I am going to
   disagree, and I think the reason is that the 28 days
   is fairly arbitrary, in my mind. I agree with
   Dr. Weinstein that as a clinician, what I look at is,
   is my patient better or not at the end of therapy.
   So that's where I would go. And if duration of
therapy is 14 days, 7 days, whatever it is, that's the timeframe that I would look at it.

DR. MOORE: This is Dr. Moore. I have to agree. Although the time-honored scenario is the 28-day assessment, I think you would have to include -- even though it may be comparing apples and oranges, I really think you have to include some earlier time points, not to the exclusion of the 28-day assessment, but some additional information for the earlier assessment, just because that's the way we practice medicine.

Dr. Follmann?

DR. FOLLMANN: I haven't really seen much data on those, so 28 days seems fine to me in the absence of data. But it seems like, in principle, we could have looked at Kaplan-Meier curves from date of randomization on out to 28 or 52 days, or something like that.

It would be helpful, though imperfect, if that was augmented sort of by cause of death as time went by. I know cause of death is very problematic really, but it's still something better than nothing.
to help address this question.

    DR. MOORE: Thank you. Dr. Neely?

    DR. NEELY: Twenty-three-and-a-half days.

    [Laughter.]

    DR. NEELY: No. My point is that I think that 28 days is somewhat arbitrary, as has been said. But if that's the only way we can get an M1, if we're going to not adopt some other approach, some other unmentionable approach. However, I really do agree with you and Dr. Chatterjee. I think we need to have an endpoint at the end of therapy.

    DR. MOORE: Thank you. Dr. Goetz?

    DR. GOETZ: Twenty-eight days, because that's where we have the best data, although it's poor in other regards. I think that the earlier time points are important, but I think that we can manage those as secondary outcomes right now rather than power our studies on that, because I don't think we know how to power studies. But we absolutely need a vigorous research path forward to find other outcomes that we can use in an expeditious fashion in that regard. I fully agree with Dr. Rex.
DR. MOORE: Amen to that. Dr. Fatzke?

DR. FRATZKE: I don't particularly like 28 days, but if that's statistically what we need, that's all I have. But we are dealing with the medically compromised individuals, and I just thought -- if it's going to have to be, to me, I would like it a little sooner.

DR. MOORE: Thank you. Dr. Fleming?

DR. FLEMING: The shorter the time period, certainly, the more likely the deaths are specifically related to the drug effect and what the drug is trying to address. The longer the time period, the larger the death rate and the likelihood to capture more fully what could, in fact, be longer-term impacts of the drug. So my sense is 14, 21 or 28 days all would have strengths and would be acceptable options to be used.

So within the two minutes, two other very quick points I said I'd come back to here, while I strongly endorse the agency's issue here that we need to ensure we're ruling out unacceptable increases in mortality, other measures as secondary or supportive
measures will be very important.

Looking at complications, empyema, meningitis, endocarditis, ARDS, time on the ventilator, time in the ICU, time in the hospital, these are all very important additional separate measures that should be considered, as would symptoms, resolving symptoms, cough and dyspnea and chest pain and fatigue.

Certainly, biomarkers are also very important for understanding the biological mechanisms, and they also should be recorded. There's no margins for these, but they're very important. And if we hit on non-inferiority and mortality and you have superiority on complications, that should be entertained as something that would go on the label. And this is surely important supportive evidence if you're going to go forward with a single trial for the strength of evidence.

Just one last thought in the last 15 seconds, and that is there hasn't been data presented over the last day, yesterday or today, that would justify a 15 percent margin within the micro
ITT setting and, ultimately, also, the margin is what we're saying it's acceptable to have, nothing less than -- anything less than that is acceptable. And I don't understand how we could argue that if it's 15 percent mortality on the active comparator, that as long as it's not 30 on the experimental, that's fine. And I've given the example already of 15 against 21.

So I didn't hear yesterday nor have I heard today an argument that says we could go above 10; 10 is generous.

DR. MOORE: Thank you very much.

Dr. Reller?

DR. RELLER: First, I'm grateful to be the last, to have the last word rather than the first to be exposed.

[Laughter.]

DR. RELLER: Considering an alternative metric, since there's two minutes a person, and it's been so efficient, by my watch, I have 32 minutes left.

[Laughter.]
DR. RELLER: Now, considerations on the timing of 28 days, we have settled on or are supportive of an odds ratio of 1.7. If I recall correctly, the number of patients that would be required to be enrolled with that odds ratio assessment would be fewer if the mortality were higher; or put another way, if it got to be very low, it would require a larger number.

I also recall that there have been multiple presentations that the difference in all-cause mortality at 14 days versus 30 days in the Niederman study that Dr. File alluded to, and several others -- but there was the general sense that two or three times as much mortality all-cause if one gets around the 28-day versus earlier. So I'm thinking in terms of a more feasible trial size number if we looked at 28-day mortality.

Now, since there is little time remaining, I would like to offer perhaps a gratuitous, but at least my own feeling about these discussion of other alternatives, including as the -- and I had the good fortune of being privy to many of the discussions as
the science has evolved from pharmacodynamics to pharmacokinetics to now pharmacometrics. And the predictive power ascribed to these techniques has become prodigious. It's even been alluded to in passing that the outcome of VABP could be associated with this. A logical extension would be why do we need clinical trials at all.

Whatever the utility is in helping to understand and inform breakpoints, and to help in the design of a good trial, they tell us nothing about safety, and I remain a skeptic. And I think it was Santayana that said "Skepticism is the conscience of science." He also said it should not be -- like virginity, should not be rendered readily.

Consequently, I think that the 28-day mortality is the appropriate endpoint and has a lot of advantages coupled with the odds ratio, and that we need clinical trials, and the emphasis should be on settling on the parameters to enable the process to move forward and getting the data, because it's a long road to get accomplished.

DR. MOORE: Thank you very much.
Okay. Let's move on to question 4. And if you could -- well, let's, if possible, have everybody address both points as they speak.

Dr. Rex?

DR. REX: So I think it's easier to deal with B first, which is to say if you're already on something and you develop HABP, what do I do about the drugs you're already on. I think that's obvious; you ignore them. If the patient developed HABP, whatever they were on, it didn't keep them from developing HABP. And so it's, yes, it is a prior antibiotic, but it is wholly irrelevant, because at this point, the patient's antimicrobial regimen needs to be redesigned. And if enrollment in a trial is appropriate, and if the monotherapy or the specific therapy that is offered in each arm of the trial is appropriate for that patient, I see no problem whatsoever with discounting entirely the prior antibiotics and bringing them into the trial, because they have, de facto, failed their prior therapy.

But A is more interesting, which is to say that they received -- perhaps there has been a period
of time during which they received therapy for what appeared to be the nascent form of the HABP/VABP, and you're now being asked -- and so they've had some course of therapy for that, and now you have identified them for a clinical trial and you're asked to enroll them. So they've actually received specific therapy that is meant to get at that.

I think there the data that we have seen to date are inconclusive; however, the preponderance of the data would suggest that a very short course of another set of antibiotics is unlikely to have an overall strong effect on HABP/VABP.

So I think like the discussion with CAP yesterday, I think there is reasonable basis for permitting a short, small number, and that number might be 24 hours, it might be 16 hours, but it can't be a lot; otherwise, it's not plausible. But I think to set it at zero is to terminate the ability to do these studies whatsoever. And I think we've heard enough data to suggest that the rate of change in bio burden is so slow that a very short course, single dose, maybe two of something else, is unlikely to
have a major impact.

   Thank you.

DR. MOORE: Thank you. Dr. Shyr?

DR. SHYR: So, again, the clinical studies without any trial. But looking at the data today from the presenter, I believe -- I forgot who presented it -- as high as 83 percent of patients who had prior antibiotic usage; the FDA review, kind of a big variation there.

   So it looks like, in general, we are facing the same problems discussed yesterday. So if we have to compromise, it's, again, feasibility and how we interpret the data. The ideal situation is to consider half-life of the drug. If you have that data, that perhaps is better than -- at least it can add more patients in the study or at least one day or 24 hours. But still, if we can have the half-life of the drug, each drug, we may have some kind of rationale to address why we include those patients.

   For the big question, yes, I think, but we may need to have more culture information.

DR. MOORE: Thank you. Dr. Calhoun?
DR. CALHOUN: So vis-a-vis part A, for a couple of reasons, I agree with Dr. Rex that 24 hours is probably the right period of time. It's consistent with U.S. practice, or maybe to put it more emphatically the other way, to exclude some antibiotics would be inconsistent with U.S. practice and probably would keep us from being able to do trials at all. And as I mentioned yesterday, I don't think it's good for the U.S., and I don't believe it's good for the agency to have all of our registration trials done offshore.

The evidence that we've seen so far suggests that there's minimal effect at the 24-hour timeframe, and so I think it's supportable from that standpoint. The concern that definitely hangs out there is that any effect that is carried over will bias toward the null and make it more likely that a non-inferiority study will be, in fact, shown to be non-inferior when, in fact, there might be a difference there. It's a small concern. I think it's one of these balances that were going to have to accept.

Vis-a-vis B, I think, again, from the
practical standpoint, if someone develops a pneumonia while on an antibiotic, it suggests, maybe, that the antibiotic wasn't effective, but there are really a lot of other potential issues here.

    Secretion control can vary hour to hour. We've gotten more aggressive in cleaning folks out and aggressive suctioning and so forth. But if you have a nurse who's a little bit not with one shift and some secretions build up, someone could potentially get an obstructive pneumonia.

    Other host factors that may come into play, failure to measure and adequately control blood glucose may induce host, defense defects and so forth. So there are a lot of reasons other than just the antibiotics don't work.

    Having said that, I don't think that those would make up the majority of the causes. And so even though I've articulated those concerns, I think probably if someone does develop a pneumonia while on an antibiotic, it ought simply to be ignored and move forward.

    DR. MOORE: Thank you. Dr. Wiedermann?
DR. WIEDERMANN: I would, I guess, reluctantly support the 24-hour cutoff, because I don't think we have any choice if we want to get some information. And certainly in terms of B, definitely we want to enroll those patients who get sick while receiving antibiotics.

I think for both of these situations, we want a very precise, unambiguous case definition, so were not quibbling over whether they have indeed HABP or VABP, and it's a new episode. And then we have to look at the organism and the therapy. Is there discordance? And you may get some ability to assess magnitude of the treatment effect by comparing patients who had received discordant therapy versus therapy that was thought to be effective.

Then as I said before, I am also concerned about not only prior therapy or therapy prior to enrollment, but concomitant therapy in the first few days of the study enrollment.

DR. MOORE: Thank you. Dr. Masur?

DR. MASUR: I think we've spent a lot of time in ICUs and emergency rooms trying to encourage
people to respond promptly when they see a life-threatening infection. So I think anything we did that delayed response I think would probably not be a desirable trial design. So to say that we will not take people into this trial if they had gotten a prior antibiotic suggests that by the time we do the informed consent and got the study drugs up, we'd be waiting a number of hours, which I don't think is the approach we really want to take.

We've, also, as discussed, heard a variety of information suggesting that a short course of antibiotics is not likely to be the pivotal event in terms of determining outcome. So I think some period of time, 24 hours, some dose where the kinetics suggest that there's not exposure for more than 24 hours would be reasonable to include in this trial. And I think for practical reasons, we just have to do that.

I think for reasons, as several people have said, we also have to start people who have been on antibiotics and are ready for a switch, that's exactly the population that we have questions about.
That’s the population we want to study, so I think we also have to include that group as a candidate, and actually a very desirable group of candidates for this study.

So that's my thoughts on those two issues.

DR. MOORE: Thank you. Dr. Bennett?

DR. BENNETT: I think HABP and VABP respond slowly to therapy, and I can't imagine that 24 hours of another antibiotic is going to seriously change the results. One of the problems in a study like this is getting the ICU docs to the hospital, or whoever, to stop the drug they're already giving. In other words, the person is already on meropenem. When you're putting them on experimental drug, you also need them to stop the meropenem, which is a bit of a challenge, and it can make it difficult to interpret results like this. It's the parallel problem of adding another drug because they don't like the way the patient looks today. So contaminating the result with ongoing drugs is more of an issue than 24 hours. I think 24 hours of a prior drug is okay.
Now, I think developing pneumonia on a drug raises an issue of the microbiology. Is it still reliable? It might end up with a microbiology endpoint having fewer patients in it because you've changed the person's flora. They may not have responded, but the flora that you're getting is now different. But I think you could take both those kinds of patients into the study.

DR. MOORE: Thank you. Dr. D'Agostino?

DR. D'AGOSTINO: It appears from the discussion that -- and my feeling is that we're going to be very careful, or one has to be very careful as you write these into the protocol what's acceptable and what isn't acceptable. But it does sound for A that there's a reasonable time, or 24 hours, that you can move them into the study, and for B that, there's less of a problem here, and you do want this patient population.

So I think that I agree wholeheartedly with the previous comments that were made and what the presentations were saying. But I do think these present a real stumbling block for the protocol that
they're fairly precisely defined, and then the
analysis follows.

DR. MOORE: Thank you. Dr. Cappelletty?

DR. CAPPELLETTY: Yes. I think the
difference between the ideal study design, which
would be clean, they're not on anything, versus
what's feasible, you're not going to get anybody into
the study if they're not on a prior antibiotic, I
don't think that I've been presented any data today,
and I don't think there's any out there that says
what's the duration that's unlikely going to confound
the outcome.

I agree we have slow resolution with HABP
and VABPs, significantly different than CAP; so the
discussion that we had yesterday with the shorter
half-life drugs and their minimal exposure and the
impact on outcome. You're dealing with an entirely
different patient population here with significant
variation in renal function. Therefore, changing
what that dose exposure timeline is, that in one
patient a single dose of a six-hour half-life drug is
going to be gone in that 24-hour timeline, but in
another patient could be the residual for another 36 to 48 hours, and is that going to have some bearing on the final clinical outcome.

We just don't have the data to truly answer that, and there's no great way to really try to control for that in a clinical trial without making the protocol really ridiculous on what would be a pre-approved or a pre-allowed antibiotic exposure.

So I guess I'd be looking at something that's maybe less than a 24-hour allowance and put it more in terms of one to two doses in order to try to maybe try to compensate in some fashion for the renal function variations.

The part B, those who develop HABP or VABP while on treatment for another infection, I don't really have any issue with that, but the confounder to me there is are they resolving that other infection or are they not resolving that other infection.

So if they are resolving that other infection, but develop the pneumonia, again, you're looking at an agent that's probably going to have a
nice clean outcome that's going to be easily
interpreted. But if they're failing that other
infection on top of starting a new infection and
you're starting a new drug, is the new drug active
against what is causing the old infection. And
that's going to again contribute to issues with
interpreting the outcome.

So I don't see an issue with allowing them
in, but I guess I would like to see some clear
delineations as to whether they're resolving that
other infection or they were not resolving that other
infection at the time of entry.

DR. MOORE: Thank you. Dr. Weinstein?

DR. WEINSTEIN: With regard to item A, I
concur with most of the prior comments that, given
the organisms that are most likely to cause
ventilator-associated and hospital-associated
pneumonia, that 24 hours, perhaps a little less, but
24 hours seems reasonable as an outside limit for the
duration of other antibiotics.

With regard to item B, it just seems
intuitive to me that if a patient who is on -- who's
receiving antimicrobials for some other reason, some
other infection, then develops a new pneumonia while
in the hospital, that the organism causing that
pneumonia is almost certainly not one that is
susceptible to the antibiotics that are being given.
Therefore, I think those patients could be candidates
for enrollment in a clinical trial. I agree that the
protocol would have to be written in a way that would
clearly specify whether the other drug could be
continued in that setting.

DR. MOORE: Thank you. Ms. Young?

MS. YOUNG: Yes. I would answer yes-yes to
A and B, with a few caveats. Given that really what
we're trying to find in these studies is superior
drugs, albeit with a non-inferiority trial, what
consumers need and what we need to kind of move
forward is superior. So I would say that if we are
allowing the 24-hour of prior antibiotic use, we
should definitely have protocols and case definitions
that would provide evidence that this was moving
forward.

Then on item B, I would agree with
Dr. Cappelletty that we should also look at what was
going on in terms of that particular case to see if
we can kind of parse out the right population to
bring into the trial.

DR. MOORE: Thank you. Dr. Chatterjee?

DR. CHATTERJEE: Thank you. For the A part
of the question, I'll follow-up on Dr. Cappelletty's
comments about not so much the time of 24 hours, but
the characteristics of the drug and the patient; so
the innate half-life of the drug that's expected,
renal function, hepatic function, however the drug is
metabolized. Even one dose, as we know, with certain
antibiotics can last for weeks, so it might still be
effective even though only one dose or two doses had
been given. So I think that needs to be taken into
account when the specific protocol is being designed.

Having said that, from a practical matter, a
24-hour time point seems like a reasonable one,
although my concern would be that it would be very
difficult to get somebody who is already on therapy
off whatever they're on and put them on an
experimental drug within a 24-hour timeframe. I
think that's a difficult sell from an ethical and, again, practical standpoint, trying to convince our colleagues who are really managing these patients that they should enroll these patients in these trials.

The second part of the question, I concur with some of the comments made already with regard to if somebody failed therapy, basically they're on therapy for whatever other infection and they now have a pneumonia, and we've confirmed that they have a pneumonia, obviously, whatever therapy they were on is not working for pneumonia, that's why they got it.

So it seems intuitive that we would allow those patients into the trial. But, again, I think we need some flexibility here to try and determine what the potential organism was that they were being treated for, what the other infection was, et cetera, before we can make a blanket statement to say, yes, it's okay for anybody who fails therapy to get onto this trial.

In terms of scenarios, the alternate infection could be other serious infections, blood
stream infections, SSIs, wound infections, et cetera, for which the person may be getting antibiotics which clearly haven't prevented the pneumonia from occurring.

DR. MOORE: Thank you. This is Dr. Moore. So I agree with the comments that have been made so far, and that is that it seems reasonable to allow the inclusion of patients who receive 24 hours of antibiotics. I think even 36 hours would be fine, as was suggested by the IDSA. But I think really it would be easier to say 24 hours for ease of use of empiric antibiotics for HIV, PRV, AVP. I think that's acceptable.

With regard to B, I'm in favor of allowing patients -- as was said before, allowing patients into the studies who have received antibiotics for any other -- no one on the ventilator, generally -- I shouldn't say nobody, but almost no one on a ventilator is not on some antibiotic. And to then develop pneumonia on the ventilator, one has to assume that whatever they have received is ineffective. If you can sort out the difficulties in
determining what's colonizing, that colonizing agent, what's actually truly causing the infection, it seems like you ought to be able to allow inclusion of those patients and go forward with enrollment.

That's all I really have to say.

Dr. Follmann?

DR. FOLLMANN: Regarding part A, unlike with CAP, we don't really have data here, and so it requires judgment. I don't really have much judgment about that. So to just amplify, I think, on a comment John Rex had earlier, which is -- and sharpen his point, I guess, which is the question really to me is if you have an experimental drug which is truly not so good or inferior, the concern is that short course plus the inferior therapy would result in the patient living by 28 days, whereas if we just got the inferior therapy, would die by 28 days. So if you think that short course is enough to change the ultimate outcome of the substandard therapy, then you shouldn't allow it. I'm just trying to sharpen the point that John made earlier about whether is it the dose itself or it's really the dose plus the
subsequent therapy.

In part B, I don't really have a problem with allowing such patients in a study. They should be involved in the study if they can contribute to answering the question.

DR. MOORE: Thanks. Dr. Neely?

DR. NEELY: I agree in principal with Dr. Cappelletty and Dr. Chatterjee. I think it would be hard, though, to operationalize that without measuring the drug concentration of a prior antibiotic or empiric antibiotic. So I think 24 hours is probably a reasonable surrogate for most patients. And I think, as has been already said, to be on prior antibiotics and develop a pneumonia, I think those prior antibiotics can be largely ignored.

In the last one minute, I just wanted to respond to Dr. Reller. I hope I didn't overstate my case. I think the proper role of pharmacometrics is to inform clinical trial design, not to replace good clinical trials. All models are wrong, some are useful, and one of the benefits of doing a trial with some modeling at the beginning is to find out if you
have a useful model.

    DR. MOORE: Thank you. Dr. Goetz?

    DR. GOETZ: Yes. I'm going to concur with everybody else who said that 24 hours of prior antimicrobials are appropriate based on the nature of the microorganisms found in people with ventilator-associated pneumonia, which are not as rapidly killed by our antimicrobials, the very high inoculums, the biofilm considerations. I think it's going to be very important, though, to ensure that we do everything possible to -- even though the organisms are relatively more resistant -- to try to get microbiological specimens from our patients before they get that first dose of antimicrobial therapy.

    Very clearly, in these sorts of trials, it's going to be very important to be working with our ICU doctors, and I think, quite frankly, they will likely be the principal investigators for our sites, because they see the patient long before -- far too long before I see the patient, as a general rule --

    [Laughter.]

    DR. GOETZ: -- quite frankly. That's a
little bit of editorial comment.

Then we get to the question that some of the original documents that were sent by the FDA, there was a suggestion that patients would not be allowed on these studies if they had received any antibiotics in the prior 30 days. I think our whole discussion says that that concept is out the door and is completely unsustainable.

So far as persons developing pneumonia while receiving antibiotic therapy, I concur that they should be eligible, but we may need to look at what antibiotics they are receiving to treat their concomitant infection. There will have to be protocol-specific considerations as to what drugs might so confound analysis that we simply can't allow that ongoing infection to be treated as it has been.

DR. MOORE: Thanks. Dr. Fratzke?

DR. FRATZKE: Since I take on the role of the patient, if I'm the patient and I'm on a vibrator -- or not vibrator.

DR. MOORE: Vibrating bed.

[Laughter.]
DR. FRATZKE: Okay. If I'm on there, and I'm developing pneumonia, I want to get started with treatment. I just heard today how important it is, and the speedier we get started on treatment, the better it is.

So I think that if there's another something to be started on, I think that should be done, because they certainly don't want to wait and have to go through informed consent and find a culture specimen, and the rigmarole of getting started. So I am definitely for starting on the original -- another antibiotic for the 24-hour period. And then I'm along with Dr. Cappelletty on B.

DR. MOORE: Thank you, Dr. Fratzke.

Dr. Fleming?

DR. FLEMING: Dr. Reller, I can give my answer in two minutes. Does that mean you're going to take 60 then?

[Laughter.]

DR. MOORE: Actually, he has 80.

[Laughter.]

DR. FLEMING: I'd like to also start with
part B. I thought that might be the easier part when I first looked at this. What about if you're taking antibiotics for other infections, and I thought the FDA was very thoughtful in saying, well, if the organism that the patients have is now resistant to the current treatment and not within the spectrum of the current treatment, than this would make sense, this would be fine.

Then as I've looked into it, my understanding is what's common in the ICU setting is we're taking these antibiotics for things like central line-related bacteremia, which might be a staph aureus, which is related to what we want to deal with here in pneumonia, or a related urinary tract infection and a Gram-negative e. coli. So it doesn't seem like it's matching the way we would want it to match.

So I guess the first part of my answer is for both pre-treatment for other infections or empiric or concomitant, my sense is we won't achieve the ideal setting here, although whatever could be done that would minimize antibacterials with
overlapping activity, to the extent possible, realizing it won't be full, would be advisable. And it looks like from the trials we've seen, there's quite a range of what can be done. So it is achievable, I would think, for us to be able to at least minimize.

Having said that, this is permissive for reasons that probably are unavoidable. But given that it is, it truly points out the influence on margins and how we choose margins; because, in essence, what we're really saying when we set up a margin is what is the effect of the active comparator, in addition to everything you're getting, including the pre-randomization antibiotics and the concomitant antibiotics. And to argue that those things don't matter on how much added benefit the active comparator, we have no -- in fact, I would strongly suggest we have evidence to indicate it will matter. I just don't know how much.

But the impact of that then is we can't be talking 15 percent margins if we're going to be permissive in this area, which we need to be in order
to make these trials feasible and achievable. It points out, again, the wisdom of the careful discussion that's gone before us the last day about the importance of care in choosing the size of the margin.

Another quick thought. I think it's important to have, as was just stated a moment ago, the base line microbiologic specimens. And I would suggest that we also ask for some specification of the intended concomitant regimens. Not that we're holding you to that, but with what's pre-specified, this enables us then to do supportive analyses in valid subgroups.

Valid subgroups are subgroups that are defined on what's known at baseline. We can't do subgroup analyses based on what's known that's actually influenced post-randomization, because that could be treatment-related.

So to facilitate the ability to understand what is the influence of these other meds, it's going to be very important to have the baseline microbiology specimens and some specification of the
intended concomitant meds.

The final thought is the FDA said what other information would be useful to address this question, and they mentioned their plans to review the available HABP/VABP data for evidence of the impact of prior and, I would argue, concomitant antibiotics on mortality. And with the kind of information I was mentioning, if this were available across trials, it would facilitate those kinds of additional exploratory analyses.

Maybe 58 minutes you get.

DR. MOORE: Thanks. Dr. Reller? Yes, you actually do have -- yes, well, a lot, 81 minutes.

DR. RELLER: I'd like an hour and 20 minutes.

[Laughter.]

DR. RELLER: First, I appreciate Dr. Neely's clarification, which actually I think, brings us into pretty much full agreement about a role and utility. Question 4-A, as strong as yesterday I was an advocate for clinical endpoints and not mortality and no antibiotics at entry, I'm in full support of
24 hours or less, particularly with the hospital-acquired bacterial pneumonia.

When we come to ventilatory-associated pneumonia in part B, realistically, the importance of getting a pathogen is crucial. And I could even conceive of a longer period if the antimicrobials given were assessed by pharmacometrics that they should be ineffective, despite if one looked at the only parameter of being the MIC, theoretically, active against the putative pathogen.

So one might have an organism that was an enterobacter that was pure, predominant, 3 or 4 plus, seen on Gram-stain smear, and it just met susceptibility, but, in fact, the patient was clinically deteriorating, and the dosing of whatever it was, was inadequate.

Now, if the organism isolated was clearly resistant to what's been given and one wanted to enroll a patient, and this would realistically be done after the fact if one had the twenty -- but sometimes the patient is on therapy, you don't know whether it's going to be effective or not. They may
even be stable, but one gets back an organism that is clearly resistant to the antimicrobials being given, that's going to take a little time. And it might even take as long as 48 hours or 72 hours to have confirmation that the organism isolated is flat-out resistant to what's being given.

Those people, it seems to me, should be enrolled, or could be enrolled, and would provide valid information, particularly if the trial design was to have a requirement that the study drug and the comparator, that one is seeking to have this tighter margin of accountability for non-inferiority, in part, with the odds ratio and to account for changes in mortality rate, that there be an obligation to rely on that drug alone for ventilator-associated pneumonia. And any other antimicrobial being given would have to be clearly, one, not active against the putative pathogen in the ventilator-associated pneumonia, and, two, be given for an indication other than the pneumonia; that is not complementary therapy or safety therapy; what if it becomes resistant, and two drugs are maybe better than one to prevent
emergency resistance?

In other words, you would be putting the pressure equally on both the comparator and the study drug to be the reason, from the antimicrobial or from an infectious disease standpoint, that there was success in the patient inasmuch as the infection was the cause of the problem.

I don't know if I'm making myself perfectly clear, but I think that one could enable a longer period of time if the therapy at the time that one initiated putting patient on study, if it was shown to be ineffective in dosage or intrinsic activity, and that from that point onwards, when entered into the trial, you were relying on the study drug or the comparator alone rather than any noise in the background; so a little more flexibility on the front end to encourage enrollment in order to have more rigor imposed on the rest of it, especially when we're considering the 28-day all-cause mortality as our primary endpoint.

DR. MOORE: Thank you, Dr. Reller.

Dr. Cox, you had some comments?
DR. COX: Yes, two things. So, first, I wanted to start out by recognizing Drs. Goetz, Follmann and Rex for their service to the Anti-Infective Drugs Advisory Committee. They're up to their term at this point, and we want to thank them for their service, and appreciate your dedication and commitment. It's a tremendous responsibility and commitment to come and join us for these committee meetings. We greatly value your input. So thank you very much for your service.

[Applause.]

DR. COX: And then I also want to extend those thanks to the entire committee and all of those that came to join us. We really do value your time, your thoughtfulness, your willingness to join us. It's very valuable to us. So thank you all. We really do appreciate it.

Back to you, Dr. Moore.

Adjournment

DR. MOORE: Well, I want to thank you, as well, Dr. Laessig, Dr. Parley and Dr. Toerner, for coming and putting all of the effort that you have
into the presentations, and Dr. Komo, as well.

I want to say I've particularly enjoyed working with Drs. Rex, Goetz and Follmann, and I know I've leaned on Dean quite a lot in past committee meetings as my go to stats guy.

Anyway, thanks so very much, everybody. And we're going to adjourn a bit early, if no one objects. Thanks again.

(Whereupon, at 3:46 p.m., the meeting was adjourned.)