FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

THURSDAY, NOVEMBER 3, 2011

8:00 a.m. to 5:30 p.m.

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

DESIGNATED FEDERAL OFFICER (Non-Voting)

Minh Doan, Pharm.D.

Division of Advisory Committee and Consultant Management
Office of Executive Programs
Center for Drug Evaluation and Research

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Diane Cappelletty, Pharm.D.

Associate Professor Pharmacy Practice
University of Toledo College of Pharmacy
Toledo, Ohio

Dean Follmann, Ph.D.

Assistant Director for Biostatistics
Chief, Biostatistics Research Branch
National Institute of Allergy and Infectious Diseases/National Institutes of Health
Bethesda, Maryland
Matthew Goetz, M.D.
Professor of Clinical Medicine
David Geffen School of Medicine at UCLA
Chief, Infectious Diseases Section
VA Greater Los Angeles Healthcare System
Los Angeles, California

Thomas Moore, M.D.
(Chairperson)
Chairman
Department of Infectious Diseases
Ochsner Health System
New Orleans, Louisiana

Michael Neely, M.D.
Assistant Professor of Clinical Pediatrics
Division of Pediatric Infectious Disease
University of Southern California
Keck School of Medicine
Los Angeles, California

A Matter of Record
(301) 890-4188
Kent Sepkowitz, M.D.
Vice Chairman
Clinical Affairs Director, Hospital Infection Control
Memorial Sloan-Kettering Cancer Center
New York, New York

Melvin Weinstein, M.D.
Professor of Medicine and Pathology
Chief, Division of Infectious Diseases, Allergy & Immunology
UMDNJ-Robert Wood Johnson Medical School
Director, Microbiology Laboratory
Robert Wood Johnson University Hospital
New Brunswick, New Jersey

Kathleen Young
(Consumer Representative)
Executive Director
Alliance for Prudent Use of Antibiotics
Boston, Massachusetts
TEMPORARY MEMBERS (Voting)

John Bennett, M.D.
Head, Clinical Mycology Section
National Institute of Allergy and Infectious Diseases/National Institutes of Health
Bethesda, Maryland

William Calhoun, M.D.
Renfert Professor in Internal Medicine
Vice Chair for Research
Department of Internal Medicine
University of Texas Medical Branch
Galveston, Texas

Ralph D’Agostino, Ph.D.
Professor of Mathematics, Biostatistics, and Epidemiology
Boston University
Boston, Massachusetts
Thomas Fleming, Ph.D.
Professor of Biostatistics
University of Washington
Seattle, Washington

James F. F. T. c. k e. , D. M. D.
(Patient Representative)
Portland, Oregon

Henry Masur, M.D.
Chief
Critical Care Medicine Department
National Institutes of Health Clinical Center
Bethesda, Maryland

L. Barth Reller M.D., D.T.M.&H.
Professor of Medicine and Pathology
Director of Clinical Microbiology
Duke University Medical Center
Durham, North Carolina
Allen Roberts, II, M.D., F.A.C.P.
Associate Professor of Medicine
Attending Physician, Pulmonary, Critical Care, and Sleep Medicine
Georgetown University Hospital
Washington, District of Columbia

Yu Shyr, Ph.D.
Professor and Chief
Division of Cancer Biostatistics
Vanderbilt University School of Medicine
Nashville, Tennessee

Bernhard Wiedermann, M.D.
Professor of Pediatrics
George Washington University School of Medicine and Health Sciences
Attending, Infectious Diseases
Children’s National Medical Center
Washington, District of Columbia
ACTING INDUSTRY REPRESENTATIVE TO THE COMMITTEE

(Non-Voting)

John Rex, M.D.

(Acting Industry Representative)

Vice President, Clinical Infection
AstraZeneca, Alderley House
United Kingdom

GUEST SPEAKERS (Non-Voting, Presenting Only)

Barry Eisenstein, M.D., F.A.C.P., FIDSA

Senior Vice President
Scientific Affairs
Cubist Pharmaceuticals
Washington, District of Columbia

Thomas M. File, Jr., M.D., M.Sc.

Chair, Division of Infectious Disease
Summa Health System
Professor, Internal Medicine; Master Teacher;
Chair, Infectious Disease Section
Northeast Ohio Medical University
Rootstown, Ohio
Jeff Dubin, M.D., M.B.A.
Vice Chair
Department of Emergency Medicine
Washington Hospital Center
Washington, District of Columbia

James Floyd, M.D., M.S.
Representing Public Citizen
Department of Epidemiology
University of Washington
Seattle, Washington

Diana Zuckerman, Ph.D.
President
National Research Center for Women & Families
Washington, District of Columbia

John Bartlett, M.D.
Professor of Medicine
Johns Hopkins University School of Medicine
Baltimore, Maryland
FDA PARTICIPANTS (Non-Voting)

Edward Cox, M.D., M.P.H.
Director
Office of Antimicrobial Products (OAP)
OND, CDER, FDA

John Farley, M.D., M.P.H.
Deputy Director
OAP, OND, CDER, FDA
Acting Director
Division of Anti-Infective Products (DAIP)
OAP, OND, CDER, FDA

Katie Laessig, M.D.
Deputy Director
DAIP, OAP, OND, CDER, FDA

Sumati Nambiar, M.D., M.P.H.
Deputy Director for Safety
DAIP, OAP, OND, CDER, FDA
Thamban Valappil, Ph.D.

Statistical Team Leader

Division of Biometrics IV

Office of Biostatistics, Office of Translational Sciences
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P R O C E E D I N G S

Call to Order

Introduction of Committee

DR. MOORE: Good morning, everyone.

Everyone can please take their seats and we can get started. I'd like to remind everyone who's present to please silence your cell phones, Blackberrys, or other devices if you've not already done so. We'll start as usual by going around the table and introducing ourselves. Let's start on the right with Dr. Rex.

John, I'm going to put you on the spot.

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 in ID 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 on the committee today is that of the non-voting industry representative. In this role, I represent
regulated industry as a whole, rather than AstraZeneca Pharmaceuticals or any other specific sponsor.

In addition, I am also currently the chair of the Area -- or 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 if such issues become relevant. Thank you.

DR. SHYR: Hi. My name is Yu Shyr. I'm the director of the Center for Quantitative Sciences at Vanderbilt University. I'm also professor of biostatistics, bioinformatics and preventive medicine at Vanderbilt University.

DR. CALHOUN: Morning. My name is Bill Calhoun. I'm professor and vice-chairman for research at the University of Texas Medical Branch in Galveston, Texas. My training is pulmonary diseases and allergy immunology.

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

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

DR. BENNETT: I'm Jack Bennett. I'm an infectious disease clinician at the National Institutes of Health and chief of the clinical mycology section there.

DR. D'AGOSTINO: Ralph D'Agostino, professor of mathematics, biostatistics, and epidemiology from Boston University.

DR. CAPPELLETTY: Diane Cappelletty, associate professor of clinical pharmacy at the University of Toledo in Toledo, Ohio.

DR. WEINSTEIN: I'm Mel Weinstein. I'm an infectious disease physician, and I'm professor of medicine and pathology at Robert Wood Johnson Medical School in New Brunswick, New Jersey.

MS. YOUNG: Kathy Young. I'm a specialist in health service administration and health policy,
formerly director of planning at the Mass Hospital Association, and regulatory specialist at BlueCross, BlueShield, and president of several consumer groups, and I'm representing the Alliance for Prudent Use of Antibiotics as executive director today.

DR. SEPKOWITZ: I'm Ken Sepkowitz. I'm an infectious disease specialist in New York City and vice-chairman of medicine at Memorial Sloan-Kettering Cancer Center.

DR. MOORE: I'm Tom Moore. I'm the chair of the committee today. I'm chief of infectious disease at Ochsner Medical Center in New Orleans, Louisiana.

DR. DOAN: I'm Minh Doan, 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 in Los Angeles, and I'm an assistant professor of pediatrics.

DR. GOETZ: I'm Matt Goetz. I'm chief of the infectious diseases program at the VA hospital in Los Angeles and professor of clinical medicine at UCLA School of Medicine.

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

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

DR. ROBERTS: Allen Roberts, professor of clinical medicine at Georgetown. I'm a practitioner of pulmonary and critical care.

DR. RELLER: Barth Reller, Division of Infectious Diseases and International Health, professor of pathology and medicine at Duke University.

DR. VALAPPIL: Good morning. I'm Thamban Valappil, statistician at the Division of Biometrics here at FDA.
DR. NAMBIAR: Sumati Nambiar, deputy director for safety, Division of Anti-Infective Products, FDA.

DR. LAESSIG: Katie Laessig, deputy division director, DAIP, CDER, FDA.

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

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

DR. TEMPLE: Bob Temple, deputy center director for clinical science.

DR. MOORE: Thank you very much. So let's go ahead and get started.

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 at the open forum of this 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 would like to identify the FDA press contact, Yolanda Fultz-Morris.

Well, that's her name.

[Laughter.]

DR. MOORE: You can look her up. I'm sure she'll be here later.

Present? Okay.

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 voting 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 U.S.C., Section 208 and Section 712 of the 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 the federal ethics and conflict of interest laws.

Under 18 U.S.C., 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 U.S.C. 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 for the development of
anti-bacterial drugs for the treatment of
community-acquired bacterial pneumonia and the
draft document entitled, Guidance for Industry:
Community-Acquired Bacterial Pneumonia, Developing
Drugs for Treatment, published in 2009, March.

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. Barry Eisenstein is employed by Cubist
Pharmaceuticals and holds stocks in Cubist
Pharmaceuticals and Eli Lilly.

Dr. Bartlett has personal and financial
relationships with Epocrates, Medscape, and
UpToDate. Medscape, UpToDate, and Epocrates provide physicians and other health professions with integrated medical information and educational tools on a variety of topics, including community-acquired pneumonia.

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 or consultant for Bayer, Daiichi Sankyo, Merck, Pfizer, GlaxoSmithKline, Nabriva Therapeutics, and Tetraphase Pharmaceuticals.

Dr. Diana Zuckerman holds stock in Johnson & Johnson. Dr. Zuckerman has been an outspoken critic at public meetings and media regarding a range of product safety and efficacy issues for J&J products, as well as other companies' products.

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, 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
they may have with the affected firms at issue.

Thank you.

DR. MOORE: Thanks, Dr. Doan.

As Minh mentioned, there will be no voting
today, but I want to emphasize to the committee
members that it will be particularly important and
helpful for the FDA to hear your rationale and your
thoughts behind a particular issue.

At the same time, there's a large committee
today, and in order to make sure we hear from
everyone in the time allotted, I'll probably have
to be a bit of a -- well, not quite a Gaddafi, but,
you know, a bit of a dictator to get people to come
to heel on their time.

So with that in mind, we'll move into the
presentations. Dr. Cox?
DR. COX: Thanks, Dr. Moore, and welcome, everybody. Thank you very much for joining us today to talk about clinical trial designs for community-acquired pneumonia. And this has been a particularly challenging area, I think, for anyone who's followed the area over the last several years, as we've tried to work through it.

I think a lot of the challenges in designing clinical trials for community-acquired pneumonia derive from, really, the biology of the infection. It's an acute disease where you have to initiate therapy promptly. And from what we've learned over the last couple years, it does appear that prior therapy can have an effect on the ability to evaluate a test drug. There's also diagnostic uncertainty at the time of patients being enrolled in the clinical trial. And one of the things that I think everybody is acutely aware of, who's looked into this area, are really the limitations of the available scientific information to try and understand the natural history and the effective
treatment for community-acquired pneumonia.

I really think, despite some of these considerable challenges, we really have made considerable progress over the last couple years, as we've tried to work through trial design issues in community-acquired pneumonia. Through the IDSA, FDA's co-sponsored workshop, advisory committees such as these, publication of the draft guidance document on community-acquired pneumonia, and also the comments that we've received on the guidance document are very helpful to us as we've tried to work through some of the scientific issues with regard to trial designs for community-acquired pneumonia.

More recently, too, there's been work through the foundations for the National Institutes of Health, in particular on the area of trial designs for community-acquired pneumonia that's helped to further move the field forward. So I think we really have moved the field forward, and I think there has been considerable progress.

No question, in the area of community-
acquired pneumonia, an important infectious
disease, it affects a number of patients every
year. And we need new therapeutic options. We'll
continue to need new therapeutic options for
treatment of patients with community-acquired
pneumonia in the future. This derives from issues
such as antimicrobial resistance, which is
constantly eroding away at our therapeutic
armamentarium, issues of patient tolerance for
different therapies, such as things like allergies,
which may preclude certain drugs from being given
to certain patients. Drug interactions can also
pose challenges when making therapeutic decisions.

In addition, adverse event profiles of
different drugs can impact upon therapeutic
decisions. And, certainly, if we can get to drugs
that either are better tolerated or that have fewer
adverse events, that's certainly a plus for the
field also. And it goes without saying, for any
new anti-bacterial drug that's developed, it's
important that we use the drug prudently in order
to be able to preserve its utility.
So what we're shooting for and what the goal is here really is to get to scientifically sound, ethical, and feasible clinical trial designs. And that's really what we're here to talk about today. There's been a lot of work in getting to evidence-based designs, and that's been particularly important in this area, where the types of trial designs that are utilized for drugs that are being evaluated for community-acquired pneumonia are non-inferiority trials.

We've talked some already about the limitations of the available information, but it's critical that we understand what the treatment effect is as we're setting a non-inferiority margin for trial for CAP.

One of the other issues that has been apparent through the comments to the docket, and, really, discussions in other fora has been the issue of feasibility and practicality of clinical trial designs for CAP.

So through the discussions today, trying to address the issues of feasibility and practicality
while still maintaining scientifically sound and ethical trial designs, I mean, that's really what will be helpful to us through the discussions today, to better understand how we get to, in essence, the area in common so that we're ethical, feasible, and also scientifically sound.

It seems to me that there are some inherent tradeoffs in the precision or the estimate with regards to efficacy and safety for a drug that are counterbalanced by some of the practicality and feasibility issues. So it's, in essence, trying to achieve a balance. And the goal is to get to feasible, practical trial designs while maintaining scientifically sound, ethical clinical trial designs for assessing both the safety and the efficacy of drugs for treatment of CAP.

Clinical trials, just looking back over the years, what we've learned from clinical trials, they really are a very important means to understand the safety and efficacy of new drugs. Sometimes we learn things that we didn't expect to learn from clinical trials, and I think that
underscores their value.

In the background document, and also you'll see in the presentations today, we'll talk about some different options. In the background document, they're numbered 1 through 3. And these are options that really focus primarily on the phase 3 development program and different trial designs. We've also tried to provide sample sizes and such so that folks have a pretty good feel for what the trial designs might be.

These are put out, really, for the purposes of discussion. We thought it would be helpful for the committee to have some ideas to react to. We certainly welcome other ideas that the committee may have about trial designs. And we really do -- we're seeking your advice today on these proposed trial designs, and then also some of the areas in particular where we'll ask for your comments. And you'll see these -- and I'll go to the questions in just a minute -- on issues related to endpoints, the effective prior anti-bacterial therapy, how that might be handled, non-inferiority
margins for clinical trials, and strategies for trying to enrich for patients who have a microbiologic diagnosis, so enriching for the micro-ITT population.

Then, overall, as we look at the options, in essence, what we're talking about is what the core of a development program might be for a drug being developed for community-acquired pneumonia.

I always think it's helpful to give a preview of the questions, even at this early point, so folks know the topics for discussion that we'll work towards, towards the end of the day. And as Dr. Moore has noted, the questions will be discussion questions, and it really is extremely valuable for us to understand the rationale and thinking that goes in. So we've got a series of discussion questions.

The first one is, please discuss the merits and limitations of an endpoint, based upon improvement in at least two of four symptoms of cough, amount of sputum production, chest pain, and difficulty breathing, and no worsening or new
symptoms, at day 3 to 5, as the primary endpoint for community-acquired bacterial pneumonia trial.

In your discussion, please comment on a non-inferiority margin for 10 percent for each of the ITT analyses and the possibility of a 10, 12.5, or 15 percent non-inferiority margin for the pooled microbiological intent-to-treat population. And this is based on the historical data of the treatment effect, the clinical response that we've seen at day 3 to 5.

So the first question deals with the endpoint and then also talks about the analysis populations and the margins. And the options 1 through 3 may provide as a useful springboard, and you'll hear more about those through the presentations that will follow me.

Question 2 talks about the endpoints. Please discuss the merits and limitations of each of the proposed development pathways and trial designs. And so this is getting to the options 1 through 3, so it's to react to those a little bit more and discuss those.
Please comment on the use of improvement or stabilization of clinical signs of pneumonia as a co-primary endpoint versus its use as a secondary endpoint. So what we're talking about here are things such as fever, and we're interested to hear your opinion on that.

Question 3, more topics for discussion. The issue of receipt of prior anti-bacterial therapy has certainly been something that's been discussed before, and there have been publications that have also talked about this issue. We're interested in understanding this a little bit more. Obviously, in the setting of an urgent illness such as community-acquired pneumonia, prior anti-bacterial therapy poses certain challenges with regards to enrollment in a clinical trial.

Methods to enrich the micro-ITT population, are there ways or strategies that can be employed to enroll more patients or patients more likely to have a microbiological diagnosis; some of the mechanisms that might be put in place procedurally to overcome some of the barriers to enrolling
patients into trials of community-acquired pneumonia. Acutely ill patients showing up in urgent need of therapy, are there certain procedural things that could be done with regard to where patients might be enrolled in trials or the procedures for enrolling patients in trials that might help to make trials more feasible or to address some of the issues of practicality.

Then we also added another question, too, and a lot of the discussion has focused on that of development of IV drugs for community-acquired pneumonia. But we thought it would also be helpful to also hear the committee's thoughts and advice, maybe there, on the issue of performing clinical trials of an oral anti-bacterial drug. And that's in the setting when an IV drug is not available.

So we've got a number of topics that we hope to hear discussion on. And I think we've got a full day ahead, and we look forward to hearing the discussion. And, again, thank you all for joining us, and we really appreciate your willingness to help us discuss and work through these challenging
issues and important area of development of drugs for community-acquired pneumonia. Thank you.

Dr. Moore?

DR. MOORE: Thanks, Dr. Cox.

Okay. Let's move onto Dr. Nambiar.

**FDA Presentation – Sumati Nambiar**

DR. NAMBIAR: Thank you, Dr. Moore.

Good morning, everybody. In the next half-hour or so, I'll quickly provide an overview of the regulatory background for community-acquired bacterial pneumonia trials. And as Dr. Cox has mentioned, we have had several discussions on this particular topic over the last few years.

So the outline of my presentation is as follows. I'll summarize the meetings we had on community-acquired pneumonia in 2008. The first meeting was a workshop co-sponsored by the FDA and the Infectious Disease Society of America. This was held in January of 2008 and was followed by a meeting of the Anti-Infective Drugs Advisory Committee in April of 2008.

I'll summarize some key aspects of the draft
guidance that was issued in March of 2009 and also
some of the comments that were submitted to the
docket. I'll then summarize the AIDAC meeting we
had in December 2009, and then close by summarizing
the comments that were submitted to the docket
since June of 2009, which is really the three-month
mark after the draft guidance was posed.

So this is a snapshot of the key events that
have taken place as these discussions have
progressed. So we first met in January of 2008,
where we had the two-day workshop. This was
followed by the AIDAC meeting in April of the same
year.

In March of the following year, we issued a
draft guidance. We received numerous comments to
the guidance, and based on the comments we
received, we brought the topic back to an advisory
committee meeting in December of that year.

In February of 2010, the FDA approached the
Biomarkers Consortium of the Foundation of the
National Institutes of Health for further
development and refinement of the endpoint, and
we're here today at our third advisory committee meeting on the same topic.

So the FDA's IDSA workshop was held on January 17th and 18th of 2008. We discussed trial design and statistical consideration in CAP clinical trials. We had a gentle discussion on non-inferiority trials. Historical data on treatment effect of anti-bacterials in CAP were presented, and there was also discussion about emerging scientific tools that might be helpful.

There were several discussions regarding the appropriate scoring system, such as the PORT and CURB-65 scores. There were discussions regarding appropriate endpoints. Some of them included mortality for severe pneumonia, a clinical response endpoint, but there were questions raised about its relationship to historical data. There were also discussions regarding the use of a patient's reported outcome tool for patients with mild pneumonia. Proceedings of the workshop were published in a supplement to the clinical infectious disease.
At the April 2008 meeting of the Anti-Infective Drug Advisory Committee, there was unanimous support from the committee members for the use of active control trials. Placebo-controlled trials were considered unethical, even in patients with mild pneumonia. There was also support for the conduct of non-inferiority trials. However, there was no consensus on the appropriate primary endpoint.

Some committee members noted that historical data on treatment effect for mortality could support a clinical response endpoint, while other committee members noted that historical data could only support an efficacy endpoint for mortality.

In general, there was agreement that confirmation of bacterial etiology provided a stronger link to the historical data. There was some concern expressed that use of anti-bacterials prior to enrollment would not be appropriate, as it would confound the efficacy findings, especially in a non-inferiority trial. We also had several discussions regarding possible enrollment of
patients in emergency rooms or urgent care facilities.

So based on all these discussions, a draft guidance was posted for public comment on the 20th of March, 2009. We did receive several comments, and comments that were submitted to the docket are available to the public at this website, and they were also appended to the background document for this meeting.

So the key highlights of this draft guidance was that the focus here was on community-acquired bacterial pneumonia, CABP, rather than community-acquired pneumonia. So the primary analysis population we recommended was patients who had confirmed bacterial etiology.

In general, non-inferiority trials were recommended, using clinical response as an endpoint. Mortality was included in the definition of clinical failures. PORT scores were recommended as an enrollment criterion, and the non-inferiority margin proposed was 15 percent for intravenous anti-bacterials and 10 percent for oral anti-
bacterials.

Superiority trials were recommended if patients reported outcome measures were being used or if a time-to-resolution analysis was being performed.

So several aspects of the draft guidance and related comments were discussed at the previous meeting of the Anti-Infective Drugs Advisory Committee. So for purposes of our discussion today, I'll only touch upon three topics which are relevant to today's meeting. And they are the primary endpoint, the primary analysis population, and the use of prior anti-bacterials.

So the draft guidance had recommended clinical response as the primary endpoint, and this was to be assessed about 5 to 10 days after completing therapy.

A patient was classified as being a clinical success if he or she were alive, had resolution of disease-specific signs and symptoms, and there were no new symptoms or complications which are attributable to CABP. To be called a failure, the
patient would have to be dead within 30 days of starting study drug, or there would have to be lack of resolution of CABP-specific signs and symptoms, or worsening of the underlying pneumonia, or need for rescue therapy with non-study anti-bacterials.

The draft guidance also recommended that patient-reported outcome measures could be used as a primary endpoint, generally in the context of a superiority trial. However, our thinking has certainly evolved over the last few years, and we are looking into the possibility of using it even in the context of a non-inferiority trial.

The draft guidance does acknowledge that, currently, there is no PRO instrument which is identified as adequate for regulatory purposes for this indication.

Now, some of the comments we received specifically regarding the clinical response endpoint are as follows. It was noted that reduction in mortality was the most clinically compelling benefit provided by anti-bacterials in CAP and that evidence-based non-inferiority margins
could only be derived for a mortality endpoint and not for a clinical response endpoint.

The primary endpoint is a composite and included components that were biomarkers. So, for example, components such as sputum color, body temperature, white blood cell count, and chest x-ray, were not direct measures of how a patient functions, feels, or survives. There was also comment that reduction in fever was a biomarker and was not a relevant clinical outcome.

So the next topic I'll touch upon is the primary analysis population. The draft guidance recommended microbiologic intent to treat as the primary analysis population. The pathogen could be identified in the blood or in an adequate sputum specimen. In addition, we allowed the use of tests such as urinary antigen test for streptococcus pneumonia.

The guidance did note that use of rapid diagnostic test for bacterial pathogens could be used; however, they would need to be discussed with the agency before trial initiation.
The reason we proposed the microbiologic intent to treat as the primary analyses population was because historical data were primarily related to patients with pneumococcal or lobar pneumonia. We do acknowledge that there were only very few patients with non-pneumococcus disease in the historical studies. However, we have found that it was acceptable to include in the micro-ITT population other etiologies such as haemophilus influenzae, staph aureus, and moraxella catarrhalis.

Some of the comments we received to this particular point really revolved around its implications on sample size. It was noted that, as pathogens are only recovered in about a third of the patients, the sample size for a trial with micro-ITT as the primary population would be large. So one of the recommendations was to use a per-protocol analysis for each trial, and to pull the micro-ITT, and consider that as co-primary.

The third topic is the role of prior anti-bacterial therapy. The draft guidance noted that,
especially in the context of a non-inferiority trial, prior effective anti-bacterials should be avoided. Two exceptions were provided. One was patients had received therapy and were considered failures, as long as objective criteria for failure were pre-specified and documented on the case report form, or if the prior therapy lacked activity against the baseline pathogen.

The guidance also noted that no concomitant anti-bacterials should be administered for other infections until after the test of cure visit. This recommendation was based on the results of the phase 3 trials, where daptomycin was compared to ceftriaxone, where prior effective anti-bacterials had a greater impact on the cure rates in the daptomycin arm. I'm not going into details of this trial, as you will hear more about it in subsequent presentations.

Again, we did receive several comments on this particular topic. One of the main criticisms was that this was an exploratory post hoc analysis from a single trial and that the finding only
applied to anti-bacterials with greater potency and
longer half-life; so one recommendation was that we
should allow the use of a single dose of a short-
acting anti-bacterial. Other comments did note
that use of concomitant anti-bacterials should be
allowed, as long as there is no overlap in the
spectrum of activity.

We did receive comments that patients who
received prior effective anti-bacterials should not
be enrolled in a non-inferiority trial, as it
diminishes the ability of the trial to detect a
treatment difference, while others noted that such
strict exclusion criteria would make CABP trials
difficult and near impossible to conduct, and that
enrolling patients in the ER setting would increase
trial costs, and may not be operationally feasible.

So after we received all these comments, we
brought the topic back to the advisory committee
meeting, and this was in December of 2009. At this
meeting, the agency presented historical data for a
large treatment effect for a clinical response
endpoint earlier in the course of therapy. So
rather than at the end of therapy, at test of cure, this was at days 3 to 5, primarily in patients with pneumococcal pneumonia. We also presented limited data on clinical response in patients with pneumonia due to mycoplasma.

So this is just one of the many slides that we presented, showing that early on in the course of the disease, there was a clear-cut treatment benefit for the clinical recovery, and these were untreated patients. And in yellow and blue are patients who were treated with sulfur drugs.

This is data that we presented from Kingston, et al., from 1961, where patients were treated with either tetracyclines or placebo. And, again, treatment difference was clear in outcomes such as temperature, fatigue, malaise, and anorexia.

So the majority of committee members voted that historical data did support the use of a day 3 to 5 clinical response endpoint. And committee members who voted no did express concern that there was some lack of information, and data
on these endpoints were collected in the historical studies.

There was nearly unanimous support for the use of all-cause mortality as an endpoint. However, some committee members did express concerns about the feasibility of conducting a trial using all-cause mortality, in part in the present day.

Most committee members voted yes for the use of a micro-ITT as the primary analyses population. Again, concerns were raised that trials may not be feasible because of implications on sample size.

Most committee members agreed that patients who received prior anti-bacterials should be excluded from CABP trials. Again, concerns were raised that this would make trials difficult to conduct.

In general, there was agreement that patients with atypical pathogens should be included in CABP trials. Inclusion of legionella was okay for severe pneumonia trials and mycoplasma and chlamydia for trials in mild to moderate CABP.
There was also agreement in the use of patient-reported outcome measures in the context of a superiority trial for mild to moderate CABP.

So then we received additional docket comments. In August of 2009, we received a set of comments, again addressing issues that we've already discussed, mainly feasibility for micro-ITT population, the inclusion of atypical pathogens, and some clarification on the endpoints. In January of 2010, we received a recommendation that we could use ITT for analysis for each of the two trials and pull the micro-ITT in a non-inferiority trial. And then in August 2011, we received recommendations from the foundations of the National Institutes of Health Biomarkers Consortium. And in the next few slides, I'll summarize the recommendations provided by the group.

The Biomarkers Consortium of NIH is a public/private partnership. The FDA approached them after the December 2009 Anti-Infective Drugs Advisory Committee meeting. And we approached them
to assist us with endpoint review and potentially for the development of new endpoints for CABP trials. The project team were comprised of representatives from industry, academia, IDSA, NIH, and FDA. FDA members on the project team are non-voting. The first project team meeting was held in June of 2010.

So, essentially, the process is divided into two phases. Phase 1 is completed and phase 2 is soon to be underway. The phase 1 of the process was the retrospective data analyses, which were performed to develop a set of interim recommendations.

The project team reviewed historical data. They reviewed datasets from previously conducted clinical trials, which included two phase 3 CABP trials where tigecycline was compared to levofloxacin. The ceftriaxone data from the daptomycin CABP trial was also reviewed, and they also reviewed the analyses performed by the FDA during the review of the ceftraroline CABP registration trials.
The second phase is the qualitative research phase, where there will be possibly improvements in endpoint measures or the development of new measures. The project team did identify that there were research gaps as far as capturing all the relevant symptoms important to patients and also in the evaluation of the reliability of measurements of patient symptoms.

So this is a graph that was in the FNIH documents submitted to the docket. And this is based on data from the tigecycline study, and this represents patients combined between the tigecycline and the levofloxacin arm, where they looked at improvement in any one symptom by one point, and then the line here is improvement in two symptoms by one point. And this reflects data from patients with documented microbial etiology.

So this graph is fairly consistent with what I showed you earlier from historical data, where earlier in the course of the illness, you do see a significant improvement in symptoms.

They also looked at other definitions. So
besides the one-point improvement in two symptoms, they analyzed data based on two-point improvement in one symptom and one-point improvement in another symptom. And for both the analyses, one point I forgot to mention is that there was no worsening of any of the other symptoms.

So based on these analyses, their recommendations for an interim endpoint was symptom improvement at study day 4, which is really 72 hours after starting the study drug. And the endpoint is a one-point improvement in at least two symptoms of cough, dyspnea, pleuritic chest pain, or sputum production, and no worsening of any other symptoms. And these symptoms are scored on a scale as absent or none, mild, moderate, and severe.

The project team also noted that absence of elevated body temperature and improvement in measures of physiological clinical stability were not included as part of this proposed symptom-based endpoint. They also noted that there was need for later assessment at the end of therapy and at some point later on, off therapy.
In the FNIH document, the project team had also presented an alternative opinion. And some of the points noted in the alternative opinion are as follows: that early endpoints are based on very limited historical data, and that early endpoints are already part of the test-of-cure endpoint. It was noted that primary outcome measures should be at the end of therapy or beyond, as it assesses the durability of response and is relevant to the use of a drug.

It was also noted that the overall endpoint could include both success at an early time point and at a later time point. And there was also note that there was need for global harmonization of endpoints.

It was noted here that several recent analyses showed a correlation between drug exposure and traditional clinical and microbiologic endpoints and that currently available agents that were approved using traditional TOC endpoints could still be used as comparators in future trials.

There are some topics which were not
specifically addressed by the FNIH, and they
include study enrollment criteria, the receipt of
prior effective anti-bacterials, the proposed non-
inferiority margin, and sample size considerations.

So, in summary, I've quickly taken you
through all the discussions we've had in the last
four years or so, identified some key topic areas
that still need discussion and will come up, and we
will seek your input during the day. And these
three topics will be primary endpoint, the primary
analysis population, and the role of prior
effective anti-bacterial therapy.

I've presented to you the FNIH
recommendations that were submitted to the docket
for an interim endpoint and have also presented to
you the alternative opinion that is included in
this docket submission. Thank you.

DR. MOORE: Thank you, Dr. Nambiar.

So now, we'll proceed to the guest speaker
presentations. Dr. Floyd?

Guest Speaker Presentation

DR. FLOYD: So today I'm representing Public
Citizen, which is a national consumer advocacy organization based in D.C. with an interest in the evaluation and safety of medications and medical devices.

Here’s an outline of my talk today. First, I'll give a little background on non-inferiority trials and then talk about a few elements of these trials, as they pertain to community-acquired pneumonia.

So a number of materials are the topic of today's meeting. And, overall, I think that the recommendations in the draft guidance, the FNIH document, and the other materials are very thoughtful, and they go a long way to ensuring that these trials can actually show that new antibiotics for CAP are effective. I think that the FDA, the FNIH, and the other people who have worked on this should be congratulated for all the progress made.

So as far as trial design, there are a few options. You can, of course, conduct superiority trials comparing an investigational drug with an active control. You could do so as add-on therapy,
comparing the new drug with a placebo, in combination with something that's already been shown to be effective.

One important feature of superiority trials is that if you conduct your trial in a way that biases you towards a null finding, that's fine; that's not a problem. A less desirable option is to do a non-inferiority trial, where you're trying to show that your investigational drug is not worse than an existing therapy by some margin.

The reason that this is less desirable is that you're not actually showing that your drug is more effective or as effective; you're excluding some margin of harm. And, importantly, a lot of the design features that bias you towards a null finding in a superiority trial will actually bias you towards a positive finding in a non-inferiority trial. So it's a more treacherous design.

I'll just briefly summarize some of the important elements of doing a non-inferiority trial. These are things that everyone on the committee is pretty familiar with. First, you need
reliable evidence of a treatment effect of your active control. The next thing we do is, from this evidence, you choose a clinically meaningful non-inferiority margin that preserves some of that treatment effect.

A third element is, the trial you conduct needs to reflect the patients, the concomitant therapies, and outcome that generated the evidence for the treatment effect of the active control. And, finally, you have to design and conduct your trial in a way that minimizes bias towards a similar treatment effect because this can give you a spurious finding of efficacy.

One other thing; because it's so difficult to conclude that your new drug is effective or less harmful than an existing therapy, it requires many assumptions, which often you can't test. The key issue is not generalizability or whether the patients in your trial reflect who you treat in your practice. It's an issue of internal validity, whether your trial can actually show that an ineffective treatment is ineffective and whether
you can make a compelling case that your drug works if you have similar treatment outcomes.

So the first issue I want to mention are endpoints. So aside from non-inferiority trials, a proper clinical endpoint for an efficacy trial should measure how a patient feels, functions, or survives, and should be reliably measured. And this is in the CFR.

In contrast to a valid clinical endpoint, a biomarker is merely something that measures a biologic process. This could be a white blood cell count. This could be body temperature. It could be a chest x-ray appearance.

Now, in some cases, you can validate a biomarker to predict, reliably, a response on a clinically meaningful endpoint. And the IOM report on biomarkers and a number of other documents show how you do this, which is a pretty rigorous process.

Now, my next slide shows some examples of what happens when you study an endpoint that is not validated. I want to highlight a couple of these,
the class 1C antiarrhythmics, encainide and flecainide. And for a long time, these were thought to be effective treatments to prevent sudden death because they reduce the incidence of asymptomatic ventricular arrhythmia. And, of course, PVCs even to date predict sudden death. They suggest that patients are at high risk of this terrible outcome.

In the 1970s, the Kass trial was done to actually study the effect on a clinically meaningful endpoint, on sudden death. And, surprisingly, these drugs increased the risk threefold. And this is some of the oldest and perhaps most famous evidence of how an effect on a biomarker does not predict an effect on a clinically meaningful endpoint.

This is a very short list. There are numerous other examples of drugs that were approved because they showed a favorable response in a biomarker that was thought to show reliable effects on clinical endpoints, but then failed to when they were studied in postmarketing studies.
Perhaps the most recent example is sibutramine, which was approved for weight loss in short-term clinical trials. It was shown to reduce weight, but it was taken off the market recently because, in a postmarketing study, it was shown to increase the risk for cardiovascular events and death.

Also, in contrast to antibiotics, these are drugs were they were approved on biomarkers or purported surrogate endpoints. And postmarketing studies were done to actually evaluate the effect on clinically meaningful endpoints.

With antibiotics, if you approve an antibiotic on a surrogate endpoint or a biomarker, you won't actually have these postmarketing tests to later show whether you have an effect on a clinically meaningful endpoint, which is all the more reason you have to have the proper endpoint for the phase 3 trials for an antibiotic.

Now, in non-inferiority trials, not only do you need a valid clinical endpoint, but the effect of the active comparator on this endpoint has to be
measured reliably. Now, as described in the draft
guidance from 2009, we actually have pretty strong
evidence of a treatment effect of antibiotics for
mortality and people who are at high risk of death,
with pneumococcal pneumonia. And because of all
the work from the FNIH group, we actually have this
evidence for symptom response, too.

I don't think we had this two years ago.
This is a lot of work, and I think they show,
pretty compellingly, that there is a treatment
effect that you can measure and estimate for
symptom response. And, also, this is an early
endpoint, sometime between days 3 and 5. I think
that's important as well.

The 2009 draft guidance suggests that test
of cure, which is a subjective assessment by a
clinician, can serve as an endpoint. But I would
argue that this is poorly defined and includes
components like body temperature that are not valid
clinical endpoints. And this test of cure doesn't
provide reliable information on outcomes that
matter to patients, like their symptoms or
survival.

A little more about body temperature, I think a lot of people propose that this could be included as a component in a composite endpoint, but composite is only as good as its weakest link, and including information on biomarkers like white blood count and body temperature make this an invalid endpoint.

So now I want to talk a little bit about the non-inferiority margin. As I've mentioned, first you need reliable statistical evidence of a treatment effect for your active control, which we have for community-acquired pneumonia, both for mortality, and I think now we have it for symptom response. After that, you have to decide how much harm is tolerable, while preserving some of that treatment effect.

People have argued different margins, and I would say that it's hard to justify anything larger than 10 percent. And if you're going to justify a margin, I think you need some ancillary benefit like decreased cost, safety, some other
consideration here, because you're not showing that your drug is as good as an existing effective therapy; you're just showing that it's not more harmful by some amount, and to provide context for these numbers, because, really, this is subjective. It's clinical judgment.

I want to look at some therapies that are considered highly effective. So if you take one of the early trials of aspirin therapy for ST elevation MI, the ISIS-2, cardiovascular death was reduced by 2.4 percent.

In one of the largest trials, comparing PCI to thrombolysis for ST elevation MI, the risk reduction for composite endpoint of the meaningful outcome was 7.5 percent.

Now, these are considered highly effective therapies to the point where they're process measures for quality of care. And I would say 2 or 7 percent reductions, absolute-risk reductions, are meaningful and highly effective. It's hard to justify a loss of effectiveness for a life-threatening disease like pneumonia on an important
outcome like death or symptom response of
10 percent or larger.

So a third element is the study population.

I agree with the FDA guidance that use of prior
antibiotics should be an exclusion criterion.

Actually, I'm sorry; that's the next slide.

The patients actually need evidence of
infection with a typical pathogen, and I don't
think this needs to come from microbiologic
culture. I agree that you should use novel
methods, existing methods, like PCR and urinary
antigens. And the purpose is not to get
sensitivities. It's just to show that the patients
you're enrolling actually have the disease for
which you have evidence of effectiveness for the
active control.

Now, it follows that the appropriate
analysis population is the microbiologic intent to
treat, and this should be with an appropriate
margin.

Similarly, the patients should be at high
risk of death for the constancy assumption to hold,
and this is whether you study mortality or a symptom response. And what this would mean is basically just enriching your trial with older patients and people at high risk of outcomes, adverse outcomes.

Again, this reflects the major threat to a non-inferiority trial not being generalizability, but actually the trial having internal validity and being able to show that a therapy is effective.

So now we'll get to prior antibiotics. As I said, I agree with the FDA that this should be an exclusion criterion. Everyone here is familiar with some of the evidence from the daptomycin trial showing that giving therapy before an ineffective therapy can make your outcomes look better.

I would argue that, even without this evidence, the presumption should be that giving antibiotic therapy that's likely to be effective will bias you towards a non-inferiority finding. And, remember, you have no way of testing the assumption that concomitant therapy or even prior therapy isn't biasing your finding. You have to be
very careful in a non-inferiority trial. So given
that it seems likely that this would be the case,
you should assume this even without other evidence.

Now, I know that in emergency departments,
for a long time, there's been a process measure
where you have to give antibiotics within four
hours. And this makes it harder to enroll
patients. I agree with that, and I don't think
it's going to be easy, necessarily. But I want to
give some examples from cardiovascular disease to
show how early randomization is feasible.

So I mentioned two trials already of
landmark therapies for ST elevation MI, which is a
life-threatening disease. In the ISIS-2 trial,
which was done a long time ago, half the patients
were randomized within five hours of symptom onset,
not presentation, but actual symptom onset.

In DANAMI-2, three-quarters of subjects were
randomized from symptom onset within four hours.
And I think the most impressive of these examples
is the NINDS trial of thrombolysis for stroke.
Within three hours, all subjects actually got
therapy from time to symptom onset.

So these are people with debilitating, life-threatening diseases, and a lot of these trials had thousands of patients. So I don't think it was easy to do these trials, but it shows that it's possible to randomize people early who have a serious disease.

So also relating to the trial conduct, the use of antibiotics after randomization I think is also problematic. First, there's absolutely no reason to have concomitant therapy with your study drug at time of randomization for community-acquired pneumonia, and this should be prohibited, the reason being that this will bias you towards a non-inferiority finding.

Secondly, there is the issue of treatment failures. I understand that people will want to switch antibiotics if patients don't seem to be responding, even on biomarkers like white counts, fevers. The problem is, if you have a similar treatment effect with your experimental drug in your active control and you have a high rate of
rescue therapy with your experimental drug, it's going to be hard to conclude that your drug is similarly effective. So you may not be able to prohibit this, but it dramatically impairs your ability to interpret the findings of that trial. So that's a caveat.

So to give an example of how these different elements can bias your non-inferiority trial, I want to give an example that was discussed two years ago at an advisory committee meeting. So cethromycin was developed for community-acquired pneumonia and I think shows a lot of the pitfalls. Most of the patients enrolled in this trial were not the ones that, ideally, you'd want to include in a non-inferiority trial of community-acquired pneumonia. Half of them had a PORT score of 1. Less than a quarter had evidence of infection with a typical pathogen for CABP, and about 10 percent received antibiotics prior to study therapy. So all of these elements bias you strongly in favor of a similar treatment effect.

Now, the FDA did a very good sensitivity
analysis, where they actually restricted the study population to an ideal population, so excluding people with a PORT score of 1, excluding people with evidence of atypical pathogens, for which there is not reliable evidence for a treatment effect, and also excluding people who got prior antibiotics. And it made the treatment effect look worse. And not only did the margins look wider because of the smaller sample size, but the point estimate was worse as well. And this isn't definitive, but I think this is a good example of how if you conduct your trial and design it in a way that is susceptible to bias, you can mask an ineffective therapy.

So, in conclusion, I think that the FDA and all of you who have been working on this have made great progress in the last two to three years, deciding how these trials ought to be done. Some of the important points, you have to have a valid clinical endpoint for which you have evidence of effectiveness of the active control. You have to have a justifiable non-inferiority margin. And I
would argue, clinically, you can't justify something greater than 10 percent.

You need to study the correct population, so people with evidence of infection with typical pathogens and also who are at high risk of treatment failure. That doesn't mean that these are the people who are going to receive the drug in practice. It just means that if you don't study these people specifically, you may conclude non-inferiority when your drug is actually not effective. This is a methodologic issue.

Lastly, you have to conduct your trial in a way that minimizes bias. And this means no prior antibiotics before randomization and really limiting the use of other non-study therapy after randomization.

I want to make an analogy that I think is useful for non-inferiority trials. It's a little bit like doing an epidemiologic study. A lot of people will, at the outset, assume that your findings are not valid because you make a lot of assumptions about ascertainment of outcomes, about
confounding. But if you design and conduct your
study very carefully, you can make a compelling
case that you have a causal inference.

I think, in a non-inferiority trial, because
out of the gate things are set up to bias you in
favor of a similar treatment effect, you have to
prove that you've designed and conducted your study
very carefully in a way that eliminates this bias,
so that if you actually show a similar treatment
effect, you can conclude efficacy. And it's only
when you done all of these elements properly, that
you can conclude that your drug is not harmful by
some margin.

That's the end of my talk. Thank you.

DR. MOORE: Thank you, Dr. Floyd.

Let's move on to Dr. Dubin.

Is Dr. Dubin not here?

[No response.]

DR. MOORE: All right. We're doing great on
time. Perhaps, we can fit him in later if he
shows. We're actually supposed to take a break
after this talk, but I'll tell you what --
Dr. File, would you be ready to present a bit early?

That's fine. Let's here from Dr. File and proceed with the guest speaker presentations.

Guest Speaker Presentation – Thomas File

DR. FILE: Thank you, Dr. Moore. It's certainly a pleasure for me to be here and to present some information concerning community-acquired pneumonia. Let me just start out by saying that I'm a basic practitioner of clinical infectious diseases. I'm based in Akron, Ohio. I am chair of the Division of Infectious Diseases at Summa Health System, which is a large multi-hospital system, and chair of the section of infectious disease at Northeast Ohio Medical University. I'm here, actually, at the invitation of the American Thoracic Society and the American College of Chest Physicians.

I just want to start out with a comment that I think we're all familiar, and that is that community-acquired pneumonia is a very common and very significant infection, actually associated
with a lot of morbidity and mortality. We know there's about a million admissions per year to U.S. hospitals. And if you look -- at least data from CMS, as far as quality measure or at least outcome measure for mortality, it correlates with a mortality rate -- at least a 30-day mortality rate, of 11.9 percent. So this is very significant. And, actually, if you look over the last four or five decades, there's not been a significant reduction in the mortality for at least bacteremic pneumococcal pneumonia during that period of time.

So I think we need to look at other approaches, whether it's new antimicrobial agents, new host modulating factors, to hopefully improve that outcome. But it's not just the 30-day mortality that's significant. I just want to stress that if you look at patients who are actually admitted to the hospital and then subsequently discharged -- and this is a Medicare database -- at one year, 40 percent of patients who truly required admission to the hospital had died. Now, it doesn't mean they died of pneumonia, but it
just does indicate that patients who are admitted to the hospital for pneumonia often have significant comorbid conditions which are going to affect the outcome of patients, and it does illustrate the significance of this.

More recently, Jose Bordon, last year in 2010, published similar data from a VA database, which showed that patients who required admission to the hospital, at 30 months, there was a 50 percent mortality; so, again, illustrating the significance.

Now, it was already shown earlier in a prior presentation that there's been multiple considerations of these trial designs for community-acquired pneumonia, and I think it reflects what we said in our guidelines even over 10 years ago, actually 20 years ago, almost, that despite extensive studies, there's few conditions in medicine that are so controversial in terms of management. And, of course, we've been using antimicrobial agents to treat community-acquired pneumonia, obviously, well before there were these
well-controlled randomized clinical trials. And as has been already observed, we do appreciate that there is a benefit of antibiotics in this particular infection.

Now, I'd like to give somewhat of a personal perspective of somebody's who's been involved in clinical trials for now 36 years, which is hard for me to believe. But, actually, in 1975, during my fellowship, I was involved in clinical trials. I'm actually just showing you the report of the first trial which I was participating in and started in 1975. As a matter of fact, my fellowship was partially supported by these types of clinical trials.

But as we all know, there's a significant change in the clinical trial process over that period of time; number one, pathogens. I mean, my gosh, in 1975, we just thought about pneumococcus and maybe mycoplasma, so called atypical pneumonia. We now are certainly aware of other pathogens. We've heard about Legionella. We've heard about chlamydyphila. We're now worried, at least for the
severe community-acquired pneumonia, about MRSA, community-associated, as a significant pathogen.

Now, what's really changed significantly has been the consent process. I mean, back then, the consent probably took 10, 15 minutes. Now, for us, it takes on the average of two plus hours to obtain informed consent. I mean, when you read these 20-page consent forms, five pages of which is a HIPAA statement, for a patient to read this, and try to understand it, and get their family members to help them look through this -- and, of course, we have our study personnel and myself to help them go through this and answer questions -- it's two plus hours to obtain this. We've already heard that it's important to receive antibiotics within a certain period of time. This, obviously, is now a significant consideration. Study implementation and report forms are certainly much more comprehensive than they were 30 plus years ago.

Then we have the confounders that have already been mentioned. The timing of the initial dose is an issue, the effect of a prior dose. We
now are under pressure to get patients out of the hospital very quickly, and our average length of stay for community-acquired pneumonia is two plus days. So if we're going to require patients to have intravenous therapy for a number of days, that's going to sort of complicate that issue. Then, of course, there's the early switch from IV to oral. The majority of our patients who are admitted are switched to oral the next day. So, again, that's an issue to be considered.

Now, 30 years ago, it was primarily infectious disease, those of us doing these trials. But now, because of these implications and these confounders, it has to be done right in the emergency department. So we have to have our emergency room colleagues actively involved in these clinical trials.

Then there's this issue of community-acquired pneumonia versus healthcare-associated pneumonia, to a certain extent, we'll be discussing tomorrow. But this complicates the issue. Does the patient truly have healthcare-associated
pneumonia? Because a lot of our patients, when you
look at them, they may have been in the hospital in
the last 90 days, but it just wasn't apparent when
we initially evaluated the patients.

It's already been discussed about this
definition of community-acquired bacterial
pneumonia, and I can certainly appreciate why this
has occurred, because we want to enroll patients
that likely have bacteria, obviously, for which
there truly is going to be a benefit of an anti-
bacterial agent.

But I just want to remind us, this is not
how we treat patients. When patients present to us
in the office, in the emergency room, in the urgent
care center, I mean, there's no way we can reliably
predict, on at least clinical grounds, whether a
patient has "bacterial pneumonia," or "atypical
pneumonia," or for that matter, "viral pneumonia."

Now, hopefully, with the introduction of
molecular tests in the future and if they become
very cost-effective and available to us in a rapid
manner, maybe we'll be able to differentiate that.
But right now, clinically, we don't do that.

So, actually, as we show in our guidelines, we state that for optimal care of the patient, we are going to treat the likely pathogens, which is going to be pneumococcus, or R pneumococcus, and maybe the atypical pathogens, and haemophilus as well.

I just want to review with us that there's multiple determinants of outcome, not just antibiotics and not just specific antibiotics. It's the timing of the antibiotics. Does the antimicrobial effect have an immunomodulatory effect that might affect the outcome? How about the bacterial load? We're becoming more and more aware that bacterial load, particularly for pneumococcus, is associated with speed of resolution or outcome.

But most importantly, there are the host factors and underlying conditions. For example, as far as therapy that are host-on, we now have multiple observational studies to show that if patients are on statins, that's going to affect
their outcome for infectious diseases, and most notably, community-acquired pneumonia.

So with that as a background, let me address some of these issues that are in consideration for this committee. First of all, as far as the early time points, I do agree that these are clinically relevant if you have two different drugs. But let's say in 4 or 5 days, you have a significant difference in that one as associated with a much better outcome than the other, that is clinically relevant. It's relevant to the patient and relevant to the patient's family. It's relevant to the patient's employers. And so I agree with that.

As we've already heard, FNIH has proposed these early endpoints, with which I agree, one-point improvement in at least two symptoms, as has already been discussed. I also believe we do need to have an assessment at a later time to ensure that patients who have an early response continue to have that and are cured, essentially, of their illness.

So as far as early endpoints, this has
already been assessed. I was involved in the
ceftaroline trials. And, as you know, the FDA used
early time points to assess this trial, and it
seemed to be effective.

I would point out, however, that from a
clinical standpoint, and from our guideline
standpoint, and from talking to many of my
colleagues, they would suggest that, really, what's
more relevant is true time to clinical stability.
That's how we treat patients. That's when we
decide if we're going to switch from IV to oral.
That's how we decide if we're going to discharge
patients, although I realize that may be two days,
may be three days, may be four days. So if you
want to have a designated time period, that may be
a little bit more difficult to assess, but we need
to combine early time point assessment with a later
test-to-cure assessment.

Now, I went ahead and evaluated two studies
that were actually evaluated by FDA to look at this
early time point because I was involved in both of
these studies, both as a consultant for the design
of the study and also as an investigator. And the first is a tigecycline-levofloxacin trial, which was already mentioned, and then more recently, a ceftaroline trial.

Now, if you look at the numbers of patients on both of these, actually, if you look at the reports in the literature, integrated analysis of two studies that have very, very similar designs. They're a little bit different in that in one trial with tigecycline versus levofloxacin, it allowed for a switch to oral therapy at day 3, so that if even patients who were on the tigecycline arm -- of course, it was a double-blind so you didn't know. But it allowed them to be switched to oral levofloxacin. And I'm going to show you, there is a difference in this study as well, in one study allowing one day of a macrolide therapy.

But there is some differences in the severity of illness, at least if you look at the PORT score, because the majority of patients on tigecycline and levofloxacin were 1's or 2's -- remember, this is an intravenous hospital
study -- whereas, at least in what I'm going to
call the modified, this is not microbiologic intent
to treat, but modified intent to treat evaluable
population of over 1100 -- all the patients were
3's or 4's. And this is an amendment change,
because if you look at the ITT population
initially, this was not required, that you could
enroll PORT 2's, but this was amended shortly after
the initiation of the study. But as you might
expect, because of the difference in the PORT
scores, and of course the PORT is age-driven to a
certain extent, the mean age here was higher by 10
years than in the tigecycline arm.

Now, what about bacterial etiology? And I'm
looking at the typical bacterial pathogens as
defined in the guidance of 2009. It would be
29 percent here and 26 percent here. Now, if you
add atypical pathogens -- which I think we should
do, I think there is evidence that there is a
benefit, an antimicrobial benefit with atypical
pathogens, in deference to what Dr. Floyd said,
that there is none. Now, if he's looking at
mortality, I can agree with that. But if you look at placebo-controlled trials, one of which was just presented by Dr. Nambiar, there is evidence of a benefit effect of a drug versus placebo, at least tetracycline in that Kingston study, of patients truly having mycoplasma.

Now, I mentioned that if you look at the mortality, 30-day mortality, of patients admitted to the hospitals in that CMS data, it's 11.9 percent. But look at these studies. We don't enroll those patients that are at the higher risk of mortality. Mortality here was 2.7 percent, 2.2 percent.

Now, as we said, the FNIH looked at the four-day response of both of these studies. And, actually, this is the response that was reported by FDA, actually, in their clinical approval. So it wasn't necessarily FNIH, because this just looked at improvement by one point in one of the four symptoms, with no worsening, or at least stability, of the other four; whereas this is the criteria as was just mentioned by Dr. Nambiar, in other words,
two symptoms. So 72 percent versus about 70 percent, this is for the ceftaroline arm, and 60 percent for the ceftriaxone arm. But, remember, these were more severely ill patients.

But if we look at the test to cure, which was the standard endpoint of the studies as they were designed, 90 percent and then 82 percent versus 76 percent -- by the way, this is a clinically statistically significant difference, even though it's a non-inferiority trial.

But now look specifically at pneumococcus -- because I think we would all agree that if we isolate pneumococcus -- at least that's a valid bacterial etiology to assess, and you can see that it's 92 percent versus 88 percent, 85 percent versus 68 percent, which was also statistically significant, actually, as far as the difference. And then I'm also reporting the bacteremia response because I think we would agree that, obviously, if a patient has bacteremia and 90 plus percent was all pneumococcus, that those would be valid patients.
But look at some of these other issues. And this is a change in the handout that I submitted two days ago. But both of these studies did allow prior antibiotics, but it was less than a one-day, two-day type of drug, so a so-called shorter-acting antimicrobial agent.

I don't know how many patients were on prior antibiotics in the tigecycline study, but in the ceftaroline, the FOCUS 1 and 2 studies, if you look at the clinically evaluable population, 40 percent -- 42 percent were on or at least received a short-acting antimicrobial agent.

I said that the one trial in the tigecycline allowed a switch to levofloxacin on day 3. There was no switch allowed here. So all those patients basically were in the hospital for seven days. This was the duration of therapy.

Now, look at the patients that were enrolled in these trials in the United States. I think this is very important because I think we really need to have good enrollment in the United States for evaluation of these drugs.
So for the tigecycline/levofloxacin trials, only 18 percent, but it was only 3.8 percent in the ceftaroline trials. Now, only one of the ceftaroline trials, the FOCUS 1, actually enrolled patients in North America, the United States; the FOCUS 2 did not. But even if you look at the FOCUS 1, only 3.8 percent. And a lot of the limitations were because of some of the timing issues, the prior antibiotics, and the consent form issue. Trying to get a consent within an effective time period was somewhat difficult.

Now, as I said, the FOCUS 1 trial allowed one day of clarithromycin, which actually is a very interesting aspect because it allows us, in a unique way, to look at the potential benefit of that one day that was in FOCUS 1 versus FOCUS 2, which we are now evaluating.

But as I look at the summary of these two types of studies -- first of all, let me just review that mortality is low. It's certainly much lower than patients who are generally admitted to hospitals. But the percent of identified
etiology -- and this is important, based on how we're going to assess the numbers of patients required, based on a microbiologic intent-to-treat analysis population -- is somewhere between 26 and 29 percent of the so-called bacterial pathogens. If we allow atypical pathogens, we can get up to about 40 percent. I say a caveat about chlamydophila because I think there's a lot of question about how we identify that particular organism.

I certainly think an early endpoint is reasonable and it's clinically relevant to patients. There is going to be a prior effect of antibiotics that I'm going to show in just a second. That's already been mentioned. And we have to acknowledge that in North America, according to our guidelines, the best optimal care -- I guess that's a double redundancy, but nevertheless, optimal care involves, if we're going to use a betalactam, adding a macrolide therapy. So that is going to, perhaps, make the study design somewhat more difficult.
This just looks at the FOCUS 1 and FOCUS 2 trials. And if you look at the integrated analysis -- I mean, this is something that I don't think we necessarily anticipated -- there appear to be a benefit of ceftaroline over ceftriaxone, at least on the numbers. But there may be a biologic plausibility for this in that ceftaroline has a much greater affinity for the mutation associated with betalactam resistance than does ceftriaxone. But it was an interesting observation in a non-inferiority trial.

Now, what about effects of prior therapy? Now, I know this study, Barry Eisenstein is going to look at in much greater detail, and it's already been mentioned twice in the presentations, the daptomycin trial, where giving one dose of a "long-acting antibiotic" had an effect, as far as the outcomes. I think this is certainly biologically plausible. If you can reduce the bacterial load to a certain extent, very early, I can see how you would have a benefit.

Well, I just wanted to show you in our
ceftaroline studies, even a "short-acting
agent" -- and by that, I mean an agent that was
administered more than once a day -- appeared to
have some effect, although this was not consistent
amongst both trials, as I understand, which was
shown in the two trials of the daptomycin study.

But if you look at patients who received
prior antibiotics in the integrated analysis, for
ceftaroline, the clinical response rate was
82 percent versus 81 percent for the ceftriaxone
arm, which shows that it's fairly similar. Right?
But if you look at those that did not receive prior
antibiotics, 85.8 percent versus 74.9 percent,
which was statistically significantly different.

So I would acknowledge that there may be an
effect of prior antibiotic therapy, but at least in
these studies, in the integrated analysis, it did
not -- I think it diminished our ability to show
that ceftaroline is an effective agent when
compared to what has been the standard practice and
best practice, and that is of the cephalosporins,
and that is ceftriaxone.
What about enrichment of microbial etiology?

It's already been mentioned that the addition of molecular tests I think can be very helpful. I'm going to show you some observations we saw in an oral study looking at amox clav, amoxicillin clavulanic acid, that we can enrich I think bacterial yield by requiring certain criteria for sputum quality, and gram stain, and the use of the urinary antigen.

There is this advance urinary antigen, at least that was presented last year at the pneumococcal meetings, which suggested it's more sensitive than the presently available immunochromatographic test. That might be helpful in enriching patients for this particular pathogen.

Then there's this issue of, can the procalcitonin, this inflammatory marker, perhaps, enrich our patients as far as adding to microbiology, or at least microbiologic, or bacteriologic etiology?

Now, this study has already been mentioned in the background information presented to us.
It's the Johansson study, which was published last year, where they looked at, I guess, 184 patients, and by including molecular tests, they were able to identify a pathogen in 67 percent of the patients.

Now, a lot of these were viral, so those would not be appropriate patients, obviously, for evaluation of an anti-bacterial agent. But what it also does tell us -- and I think a lot of other studies are showing this now that we're using molecular tests -- is that about a third of the patients, even for adults, who are admitted to the hospital with community-acquired pneumonia, have monomicrobial infection with a virus. It's not a bacteria.

So I think this is going to be very important because you don't want those patients in the study. I mean, if they've got RSV, adenovirus, metapneumovirus, that's not going to be a patient for which an anti-bacterial agent should at least show a difference. Now, a lot of these patients have polymicrobial infection or mixed infections, and that would be fine.
Now, if you look at the Johansson study, interestingly, for those patients that had all of the tests done, which means standard microbiologic tests, urinary antigen tests, serology, and PCR, that, actually, 89 percent of the patients had a defined etiology. And personal communication from Rich Wunderink at Northwestern, who's participating in the CDC epi trial, where they're looking at the surveillance of all patients who require admission to the hospital and they're using molecular tests, he tells me that they've doubled their number of patients with identified pneumococcus, based on whole blood PCR. Now, I realize that that is not FDA approved, but I think it's something to look at in the future.

I mentioned that when we look at some oral studies or studies of oral agents, this would pertain, obviously, to antimicrobial agents that are just available orally or at least for outpatient studies. And I apologize. Probably the most important information here is the smallest font here, but if you look at the studies where we
evaluated actually six different trials of amox clav -- and really evaluating the high-dose, pharmacokinetically-enhanced amoxicillin clavulanic XR, if you will. But in those studies where we required positive gram stain, which meant there had to be good quality, there had to be evidence morphologically of gram-positive cocci, hopefully lancet shaped, or a positive urinary antigen, you can see that we were able to identify pneumococcus in about 20 percent of the patients, which is I think pretty good. So by requiring that type of criteria, that did enhance the microbiologic yield.

Finally, there's the procalcitonin. And in the 2008 workshop, Mike Niederman reviewed the potential for procalcitonin. He suggested that the ability of the procalcitonin, at some cutoff, may be able to predict bacterial etiology and therefore enrich patient population.

On the contrary, a very low procalcitonin would suggest it's not bacterial, so it could be used potentially to help enroll patients if you get it back in a very expeditious time manner.
Now, since that time, Dave Gilbert has reviewed many studies using procalcitonin. I'm just showing you some quotes here. But he states that it should be possible to use advanced molecular diagnostics to evaluate the ability of the serum procalcitonin to separate viral from bacterial infection.

Then more recently, just two weeks ago today, actually, Dan Musher's group presented at IDSA an abstract entitled, Procalcitonin As a Diagnostic Tool to Distinguish Bacterial Pneumonia in Patients with Pulmonary Infiltrates, and that's what we tried to do. And their conclusion was that if a procalcitonin was greater than .55, it may be useful as a diagnostic test in evaluating patients submitted with new pulmonary infiltrates. The sensitivity of that for bacterial etiology, according to the clinical criteria, was 78.8 percent.

This is just from Dave Gilbert's study, and for purposes of time, I'm not going to review it. But if you look at the studies that he reviewed
that specifically looked at pneumonia and looked at, at least the patients, how if affected therapy -- of course, they were predominantly looking at either not including therapy or shortening therapy -- it did have an effect, based on what was felt to be a differentiation of bacterial versus non-bacterial etiology.

Finally, I was asked to review some of the barriers to clinical trials. Some of those have already been mentioned. We already mentioned prior antibiotics. Certainly I think if a patient has been on prior antibiotics, and they're presenting to an ER, and they're sicker, I think we should allow them to be enrolled.

I really do feel that with the sort of dilemmas we have now, with the realization that earlier therapy is associated with better outcomes, and with the complexity of obtaining consent forms, it's going to be very difficult for us to go through the whole enrollment process within a given period of time and still give the patient timely administration of the first dose of antibiotic that
is going to be associated with the best outcome.

So I think we have to still look from a feasibility standpoint of allowing short-acting antibiotic to enrollment, and we may have to assess these somewhat differently, but that's going to be something that you'll need to discuss.

Having study personnel always in the ED I think can be helpful in, perhaps, avoiding even initial antibiotic therapy before enrollment. The timing of the initial antibiotic has already been mentioned. I will just state that as of January, that no longer will be a CMS-quality measure as far as the time to the first dose, so that is not going to be the issue. However, we do know, because of a variety of studies, that there is a benefit of earlier antimicrobial therapy, so that still has to be considered.

We're under pressure to get patients out of the hospital quicker, early IV to oral switch. So you may want to consider allowing a short course of IV and then a switch to oral therapy. That was done in the tigecycline study. At least you can
still get early time point assessment. And enriching for bacteriology, I mentioned specific criteria for sputum quality, molecular test, maybe the advanced urinary antigen test, perhaps the procalcitonin if it's validated. And I would include atypical pathogens. I think there is compelling data, at least for mycoplasma and Legionella. Now, mycoplasma may not be mortality, but certainly clinical benefit with earlier time point assessment of appropriate antibiotic versus not, and certainly with placebo-controlled trials. And then I already mentioned that the consent forms now are becoming much, much more intimidating and time-consuming.

So with that, what I would suggest is maybe the way to get around this is to -- and I know NIH is looking at this -- develop a clinical trials network based on the ACTG model. And we are sort of doing that. At least, I'm participating in a trial which is actually going to start -- we're doing the feasibility part of the trial right now, but there's five centers, in which we are one of
the centers, of an NIH-funded CAP trial -- Victor Hugh is the lead of this -- where we're going to -- the PIs are ID, ED, and then microbiology. We're all working together, but we're going to have study nurses in the ED 18 hours a day, seven days a week. That I think is the only way to do it to capture your patients right away when they come in, try to avoid, perhaps, prior antibiotics, although this, from a paradigm, is going to be much different and how it's going to be expensed has to be decided.

We're going to have a lot of rapid diagnostic tests. It's not all diagnostic tests, but we're going to do film array multiplex PCR that we're going to have available within an hour. We're going to have procalcitonins within an hour. We're going to have gram stains within an hour, urinary antigens within an hour. So we're going to have a lot of tests available in an hour.

We anticipate enrolling 6,000 patients in two years. So if we can do this and then other networks can do this, then this may be a way to do
these clinical trials as well. And there are other cooperative groups. There's the CAPO group, the EPIC group that I mentioned, which is the CDC surveillance group that is ongoing right now, and there's an ED network that may be able to do these studies.

So, in summary, we do need to do these studies. They need to be feasible. We need to be valid. It's already been mentioned. There is an unmet need. I think we need more options for community-acquired pneumonia, and we need to try to reduce that mortality rate of patients submitted to the hospital from 11.9 percent to lower.

Where we really need it -- and this addresses this mortality issue -- is in severe CAP, because that's where we don't have the clinical trials, and these are very difficult to enroll as well.

So I agree with early time point for assessment. We must accompany that with some type of test-to-cure later stage endpoint. As far as early time point, whether it's a specific day or
time to clinical stability, you can discuss that. I would consider allowing prior short-acting antibiotics based on just the feasibility of it in order to provide optimal care for patients, but acknowledge and assess that there is a potential effect of that. And maybe you could assess that differently, at least separately, to enrich microbiology with a sputum assessment, and molecular test, and possibly the procalcitonin, which I think needs more additional validation.

Thank you very much for your attention.

DR. MOORE: Thank you, Dr. File.

Why don't we go ahead and take our scheduled break? We'll take a break for 15 minutes, and then when we come back, let me have Dr. Dubin, who is here now -- yes, hi. We'll have Dr. Dubin present after the break. So we'll reconvene here at, let's say, 9:45. That's actually 13 minutes, but close enough. Thanks.

(Whereupon, a recess was taken.)

DR. MOORE: We're a little out of order, but we'll now start the sessions -- I'm sorry -- resume
the guest speaker presentations with Dr. Dubin.

Guest Speaker Presentation – Jeff Dubin

DR. DUBIN: Okay. I'll get started while people are getting back to their seats here.

My name is Jeff Dubin. I'm an emergency physician at Washington Hospital Center, which is in Washington, D.C., and we're a community teaching hospital. We're the busiest hospital in Washington, D.C. Our emergency department is certainly the busiest, the adult emergency department.

We go back and forth with Children's Hospital, who actually sees more patients. We're close to about 90,000 visits each year. And we do have residents and medical students from Georgetown who are here, but still about 60 percent or so of our patients are seen primarily by docs like myself who refer to ourselves as sort of the doctors in the trenches here in the emergency department, and I've been there for 15 years.

So why the emergency department? Why am I here? Well, we're the portal of entry for most of
the patients who are getting admitted to hospitals with community-acquired pneumonia. I think, when I first started -- I mean, I've only been out 15 years, but patients used to not have to be too sick to get admitted to the hospital. And now there are all sorts of requirements for the various insurance companies, and Medicare, and Medicaid that make you be quite ill before you actually get admitted. So these patients are either choosing to skip going to their doctor and just coming to the hospital, or they're going to their doctor, and they don't look too well. And they're actually going to the emergency department so they can get treated more quickly than just being admitted on the ward and waiting until someone sees them to start getting treatment for them.

You probably can't see too well there, but it's a patient with pneumonia on here.

So I have a very, very brief agenda here. My presentation is going to be pretty short, but I mostly wanted to talk about some of the opportunities for doing research in community-
acquired pneumonia in the emergency department and also some barriers that are out there to actually enrolling the patients because I wouldn't be truthful if I said it's going to be really easy just to enroll patients in the ED here.

We do have some problems which will slow down the process, but also at our hospital, we do enroll patients in studies that other departments are doing. They need to flag patients in the emergency department, and we have some studies where we're the primary site for doing ED studies for patients here.

So the opportunity I think is the number of patients that are out there. This is from 2008, and that was 124 million visits. It's probably 126 million or so now, an awful lot of patients are coming through the emergency department. And contrary to popular belief, most of the patients who come to the emergency department really aren't there just because they have primary care problems and they can't find a doctor, so they come in. We're an adult-only emergency department in an
urban area. Most of our patients are pretty sick. Most of them don't walk out without getting some tests or medications at some point. So this is not just your patients coming in with sore throats and stubbed toes that are coming into emergency departments these days. A lot of them are quite ill.

The number I found was half a million. I actually defer to the speaker beforehand, who seems to have a lot more experience than I in these pneumonia trials of a million patients. But either way, between 500 and a million hospital admission for pneumonia, there are a lot in the United States that are out there.

The barriers, I think, are the things that I just want to go through with everyone here. I'm just going to touch briefly about overcrowded hospitals and emergency departments, some of the centers for Medicare and Medicaid services, and the Joint Commission core measures, and how these core measures have had an effect on emergency department operations, and how they may have a lingering
effect on community-acquired pneumonia trials, which is something that you will need to keep in consideration in the future; and the prior speaker had touched upon those as well: antibiotic use prior to emergency department visits, and then some operational constraints within the emergency department that will probably affect these trials in some way.

So let's talk first about overcrowding. Hopefully, none of you have had too many experiences in the emergency department, but if you do, it's like going to a restaurant on a busy Saturday night without a reservation. You're going to have to wait, unless you're very, very ill. There are only so many beds, just so many doctors, just so many nurses. And certainly the demand for emergency department services just overwhelms the capacity for both the emergency department and the hospital itself.

The reason we like to call it, in emergency medicine, hospital overcrowding is because it's not just that the ED just can't manage these things.
What happens in the hospital is that there are not enough beds for admitted patients. And certainly, some things could go a little more efficiently. But in the busy afternoon, on a Monday or Tuesday, when there's a lot of elective operating room cases, if you're in a busy cardiac center, the cath lab is full, and you have patients who decide to put off going to their doctor until the weekend was over, they come and they converge, Mondays and Tuesdays are very bad days. And what happens is, once these patients get determined that they need to be admitted to the hospital for pneumonia, CHF, whatever illness they have, there's often not a bed upstairs for them. So what happens is they wait in an emergency department bed.

In the example of my hospital, we have about 40 beds in our main emergency department, and we're admitting probably 80 patients or so sometimes on a day. If, on a busy day, we're boarding, we have patients -- let's say we have 30 patients at peak times who are admitted, waiting to get a bed upstairs, that's taking up three-quarters of our
beds. So our emergency department, which used to have a lot of beds, now has, effectively, 10 beds. We usually have a little bit more because we'll move people into the hallways, but this is a hindrance to actually having patients come in and get seen by doctors and nurses, because most of the time, you do actually want to see a patient in a room rather than talking to them in a hallway or in a chair. And, again, these are things, when you're talking about these studies, to keep in mind, that it's not going to be a walk in the door, within five minutes see a doctor.

The Joint Commission and CMS, very good intention to core measures, to say, hey, if a person is sick and they need to get antibiotics for pneumonia, it's probably a good idea to give antibiotics sooner than later. It's a great idea, and, of course, money was tied to this, publishing these things on the hospital, compare websites, so that laypeople, when they're deciding, "Well, just in case I get sick, which hospital in the district, or Maryland, or Virginia should I go to? Let's see
who does best on the core measures for CMS."

So these are rating things that hospitals -- no one wants to be on the bottom. Everyone wants to be on the top here and meet the core measures. And everyone's trying to do what they can to hit these core measures, get paid for it, and have people want to come to their hospital.

So the core measure that's really hit the emergency departments, they called it pneumonia 5b, which was patients who come to the hospital, who are admitted with pneumonia, and need to get antibiotics within four hours.

Perhaps, from someone who's not working in an emergency department, four hours seems like a pretty long time to give someone -- to be able to walk into the emergency department, register, see a triage nurse, get an x-ray, get your antibiotics.

It is a lot of time if you think about it from the time the doctor sees the patient until the antibiotics are given to the patient. But the problem is, because of this overcrowding and too many patients coming in, there are times, and there
are a number of busy emergency departments in the
country, and mostly in urban areas, where the
demand far exceeds the supply of beds and doctors,
where it can be several hours before you can
actually see a doctor. It's not good. It's not ideal. You see these advertisements for places.
We'll see you within 30 minutes, and that would be ideal. We certainly strive for that, but we're not there. We're hoping to see people within an hour or so.

So what happens is, your first hour is lost,
or your two hours, or in some cases, three and four hours are lost, and you couldn't make this.

So this has actually been studied. There are a number of studies out showing what emergency departments did. And we tried to work with the hospital to try to limit our overcrowding, so we could free up more beds for patients go upstairs, so we could try to rapidly cycle people in and out of the emergency department.

We work with our radiologists, so whenever they see a potential pneumonia, they actually call
the doctor. So we get calls all the time. "Hey, I just saw this patient, John Doe. Looks like he's got a right lower lobe infiltrate." It's like, great, thanks. And so if I hadn't gotten a chance to go back and see that x-ray soon enough, as soon as the radiologist sees it, I know.

We've worked with our standing orders for our emergency departments for our nurses, who actually order x-rays and even get antibiotics before the doctors even see the patients. And we certainly give a lot of feedback to all our docs. At our hospital, we review 100 percent of the patients submitted to the hospital with pneumonia to see, did we meet the 4-hour, now the 6-hour, limit on that. And if not, we look back to see what the problems were.

So we're certainly geared up to try to take over -- we're geared up to sort of see people quick with pneumonia, diagnosis, and get the treatment in there, which, actually, even though I look at this as a barrier, it actually bodes very well for future studies for community-acquired pneumonia in
emergency departments because we're basically geared up for this disease, and we're trying to take care of it and diagnose it quickly.

So one of the things that happen is liberal dispensing of antibiotics for patients who have pneumonia. Like I said, we have standing orders in the emergency department for our nurses in triage. If they see a patient who's got a fever and a cough to order an x-ray and give a dose of antibiotics by mouth if they're not allergic to anything. So we typically use azithromycin because that's one of the core measure drugs that you get scored on.

So the candy jar is here because we joke around that we give out antibiotics like candy, and I'm not the first person to say that this is a bad result of the core measures. There have been articles written about this, that it's not all good. We're probably giving antibiotics to many people who don't need them.

I have a good friend who's a cardiologist who complains to me all the time about, "You guys in the ER, you're admitting all these patients with
heart failure, and you're giving them antibiotics for it. Why?" And we're like, "Well, because if the radiologist says it's an infiltrate, we're not going to take a chance. Maybe they have pneumonia and CHF."

So there's a lot of overuse of antibiotics now because of this. But, fortunately, a couple years ago, we got a little dispensation from this. We got an extra two hours. So instead of four hours to treat people, we got six hours; everyone's core. Take a deep breath. You got some more time to spare.

So as a result of this, not much changed. We're still giving out antibiotics like candy up in triage and trying to get people back quickly, and get them treated. So it's still a problem, and it becomes problematic, too -- the prior speaker had talked about the issue of antibiotics prior. We're giving antibiotics prior. When they walk in the door, they're getting antibiotics within about 15 or 20 minutes of walking through the door, and that is something to take into consideration when
you're trying to figure out what drug is going to
work best for these patients who are sick enough to
be hospitalized.

This cliche here, "the light at the end of
the tunnel," but it is there, January 1, 2012, the
six-hour window for antibiotics is actually going
away completely. And instead of being scored on
the timeliness of antibiotics in the emergency
department, we're just going to be scored on the
appropriateness of antibiotics, which is certainly
something that will be easier for us.

But the problem is we've been doing this for
years. And anyone's who's a practicing physician
or nurse knows that it takes a long time for docs
to learn new things. And so, if we've been
practicing this for eight, nine years, and then
suddenly, boom, you don't have to do it anymore,
it's going to take a while for people to stop doing
this thing.

It's certainly non-insurmountable, and I
hope that, at our hospital it's certainly no more
than six months when we stop giving antibiotics out
of a candy jar up front, but there's still that concern of, hey, you want to treat someone early and not leave them out lingering so you're waiting to make your final diagnosis, whether it be by x-ray or CT scan.

The prior antibiotic use, in addition to what we've been doing in the emergency departments, there's certainly concern about people out in the community giving antibiotics to all those folks with colds, who then maybe develop a true pneumonia after that, or maybe they started out as community-acquired pneumonia. They tried oral antibiotics. They were a failure to treatment, and then they're coming to the emergency department. Maybe they've been on amoxicillin, azithromycin, or another drug for a few days, and is that going to cause problems with the study?

I really don't think it's that big of a problem. The majority of the patients that we see who are sick enough to get admitted to the hospital with pneumonia, they usually haven't seen a doctor. They're pretty sick when they decide to show up in
the emergency department. Again, one thing we've noticed a lot is, a lot of our patients actually have doctors.

Part of the reason they come to the ED is because we're convenient. The doctor's office is closed at 4:00 or 5:00. They call. They can't always get appointments because primary care doctors, at least in D.C., there's actually not enough of them. They're very busy. They're overbooked. They can't see the patients; or the patients just decide, you know what, I got this terrible cough, and I'm short of breath, and I got a temperature of 102. What's my doctor going to do? Send me to the emergency department? Why should I take two visits?

So they're actually coming to us de novo. And so most of the patients that I've admitted don't have prior antibiotic use, so I don't think it's really that much of a problem.

Some of the operational constraints, in addition to the crowding emergency departments, the docs themselves are trying to work very hard to see
as many patients as possible. We get measured on
lots of things, more than just the core measures.
As docs, we have to look at our productivity.
We're looking at how long it takes us to actually
make a disposition. In the emergency department,
the disposition is as important as the diagnosis.
Is the person going to go home? Are they going to
get admitted? And how long is it taking you to do
these things? How many resources are you doing?
You don't want to order a lot of CAT scans because
we're trying to minimize the number of CTs we're
doing. We're trying to minimize the number of x-
rays that we're doing.

So the docs are all focused on these things,
and if you want them to sort of stop in, enroll
someone for two hours for a trial, that's just not
going to happen. So when you think about these
trials, certainly you want to find the patients in
the emergency department, identify them, but we
want to work on ways that the ED docs working in
the pit here can just quickly identify the patients
and then have someone else come in and do the rest
of them, and also have it go quickly; because if it
takes two hours to enroll a patient, and then we're
trying to get the patients admitted and everything
set up within a few hours also, that's just adding
more and more time to making our final disposition
of the patient.

You really need to get buy-in from the
stakeholders. And the key stakeholders enrolling
in these studies are we, the ED docs. We're the
gatekeepers for these folks. We're trying to
decide who are we going to call the study
coordinator for, who we're going to get admitted,
who's going to stay home. So you want to make sure
that whatever study is done, the ED docs are really
involved with this stuff and are happy with the way
it's going to not impede their workflow.

Believe me, we want to have patients on the
appropriate drugs. We want to have them treated.
And we want to have them get into the hospital, get
better, go home, and not come back in 30 days also,
because then we're going to get a letter from CMS
saying that we had a re-admission for 30 days, too.
So we want to make sure that the drugs work, they work well, they work effectively, and we're identifying the right patients for you.

The opportunity is the numbers of patients, over 100 million patients. And we're open all the time, so patients are not getting sick Monday through Friday from 8:00 to 4:00, when they present to the primary care doctor. They're getting sick at all hours. We start ramping up for business at about 10:00 or 11:00 in the morning, and we really start decreasing around 8:00 to 11:00 at night. In our hospital, we're pretty much quiet only from about 2:00 in the morning until 5:00 in the morning.

So the speaker before me had mentioned having research coordinators in the ED 18 hours a day. That's great. We're doing a study right now; we only have research coordinators available from 8:00 until 4:00, and we've actually missed several patients to enroll already -- this study started a week ago -- because they're presenting after 4:00.

So it's really, really important, if you
want to get these patients, to make sure that you've got the funding for the resource granters to be around in the late hours, because patients may decide, "I'm going to go to work, and I'll bear out this cough." And then, "I'm feeling really terrible." They get home, and their family member says, "You know what? We got to take you to the emergency department," or they wait until their kids get home from school, or someone can watch their kids; then they go to the emergency department.

So you really want to make sure that your model for enrolling patients is as close to 24/7 as possible. Maybe you don't have to do the weekends, but I certainly would do the weekday evenings on these folks or you're going to miss them.

What we found successful at our hospital is just a simple call. You've got one phone number, a cell phone, or a pager number. All the docs have to do, or the nurses even, is say, "Hey, this is a potential." We call the study coordinator. They may not even be in the emergency department. They
may be in an office somewhere in the hospital. And they're able to come down, and evaluate these patients, and enroll them.

Again, even though I was sort of pointing a little bit of fun about CMS and the Joint Commission about these core measures of being not realistic expectations for what can be done in the ED, as a result of these ones, we're really good at picking people out with pneumonia pretty well, or at least identifying potential pneumonia patients from the get-go, once they come in through triage.

One of the things that a lot of hospitals have done because of the crowding and to meet some of these core measures -- and we do -- we actually have a doc in the emergency department in front of triage for nine hours a day on weekdays, sitting out there, seeing patients within 10 to 15 minutes of arrival, and looking at them quickly.

So we've got a doc, not just a nurse out there, who can make a quick call to study coordinators and say, "Hey, I just saw this patient. Good story for pneumonia. And they look
like they're probably sick enough to get admitted
to the hospital," and get those folks down there,
in there.

The nurses alone are actually, in addition
to looking for pneumonia, where they're just
handing out antibiotics and x-ray slips for
now -- but we're also looking at strokes and acute
MI. And that's another very, very time-sensitive.
For acute MIs, we want to try to actually have them
identified and out of our emergency department to
the cath lab within 25 minutes of arrival.

So they're really looking at these time-
sensitive issues here. So we're geared up for
this.

So, in conclusion, a lot of the patients who
are sick enough -- and you're looking at people
with high PORT scores, older folks, people who are
going to be admitted -- they're really self-
selecting to come to the emergency department.

So we're seeing them. We're seeing the
majority of them. Even if they show up at a doc's
office or a clinic, most of the ones that are truly
sick are not being told to just go to the floor and wait for a reservation in the lobby, and you'll get your room eventually, and get your antibiotics. They're coming to us, and we're seeing them, and most of them are not having the antibiotics prior.

Despite these operational challenges, the overcrowding, all the core measures, the other measures that the docs and nurses are being looked upon, and the challenges of not having enough beds, and people to see these patients, we're really in a good spot to enroll these patients. And I think you'll certainly be successful in looking at the ED as the enrollment spot for patients these days.

I'll take any questions if people have them.

DR. MOORE: Actually, we'll do some questions at the end. Thank you, Dr. Dubin. I appreciate that.

Let's move on now to Dr. Eisenstein, who will be representing PhRMA.

**Guest Speaker Presentation - Barry Eisenstein**

DR. EISENSTEIN: Dr. Moore and others, thank you for inviting me to present. I am representing
PhRMA Industrial Consortium. I chair a committee on emerging pathogens for PhRMA. I also work at Cubist Pharmaceuticals, and I'm going to try to respond to some of the questions in the briefing document.

The key observations that I'd like to start off making, regulatory uncertainty and feasible study requirements decrease the likelihood that our patients will have needed new antibiotics in the future. This mirrors what Dr. Cox began his presentation with.

We support trial designs that are ethical, scientifically valid and feasible, that are optimally informative for prescribers, which includes, of course, prescribers in the United States, and that becomes an important aspect of the rest of my talk as well.

They also need to harmonize with regulators internationally because most of the approvals are meant to be for international use, that employ the best locally recognized standards of good clinical practice. And this gets us into the issues that
we've just heard previously, about the need for very rapid antimicrobials when patients are first seen in the emergency room.

There needs to be a balance between data quantity and quality, something that is, perhaps, forgotten. We also think that the March 2009 draft guidance on pneumonia and the recent FNIH work that I have also been part of on endpoints establish some good, common ground, and we'd like to then elaborate beyond that.

So our key recommendations, number one, clinical response should be the primary endpoint. Test-of-cure evaluation at 3 to 7 could be 5 to 10 days after end of treatment. That would be study day 13 to 15. The point is to be able to assess the patient after antibiotic is no longer in the system, and there's the opportunity to see whether relapse is going to occur.

As has always been the case, failures at study day 4, i.e. after 72 hours of treatment, are carried forward. This carries, then, the assay sensitivity that's been well explored with the FNIH
We believe that the intent to treat or possibly the clinically evaluable or per-protocol population, the EMA seems to be more in favor of that smaller population. It should be the primary population for analysis. We think that, under certain circumstances, a single phase 3 trial could be employed. Age we believe is the key severity inpatient selection attribute. And as has already been stated, age is the major driver behind the PORT and CURB scores anyway.

We do feel that short-acting prior antibiotics for less than 24 hours should be allowed under appropriate circumstances. We believe this is a key element to enabling feasibility of trial design.

So to specifically, then, address the three questions, question 1, please disease the merits, limitations of endpoint based on improvement, et cetera, we feel that this approach makes very good biological sense. These measures capture the sense of early failure that has been present and
has essentially been used in every antibiotic registration trial we know of insofar as standard clinical practice incorporates this evaluation.

Patients not improving at this point are often switched to different treatments, which is why all prior pneumonia trials have been good trials, because they've essentially incorporated that attribute. However, late endpoints are important, too.

Just to briefly review some of the aspects of the FNIH review, I'm not going to go into great detail here, but it's quite clear from the prior antibiotic era, or the pre-antibiotic era, and then the early antibiotic era, when antibiotics were first introduced, that there's a very significant improvement that does occur on day 3 and 4. This has already been reviewed by several of the previous speakers. This is quite apparent and provides enormous validated assay sensitivity. We, therefore, support the FNIH recommendations to incorporate evaluation at study day 4 within the trial design.
We feel that the early clinical effects are quite powerful. However, later endpoints have meaning as well, and we've already heard from prior speakers that they incorporate later endpoints into their evaluations.

Overall drug efficacy is what we're really trying to think about here. To do a thought experiment, if you had an antibiotic that had extraordinarily high anti-inflammatory capabilities but was perhaps only bacteria static, you might imagine getting very good results at 3 to 4 days, but actually not as good results against a bactericidal antibiotic at the end of therapy. That's just one potential thought example I can come up with.

But other examples demonstrate, from the literature, initial improvement -- this is from an actual early case report in the literature, initial improvement with sulfapyridine, followed by persistent fever due to an empyema that evolved. Drug treatment made the patient feel better, but the patient later failed. And you can go through

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this description. It's quite colorful, and those of us who practice medicine have seen this in our practice.

So in terms of the primary endpoint, what endpoint should be used in clinical trials for community-acquired pneumonia? We believe that the clinical response, as proposed in the March guidelines, make the most sense. Mortality alone should not be the primary endpoint for non-inferiority trials because we're talking about mortality rates in the 2 to 3 percent range, which essentially makes it very difficult to be able to see a non-inferiority margin.

That's not to say that mortality should not be looked at very carefully. And if there is a mortality imbalance, this obviously calls into question, severe question, the efficacy and safety of the drug that's coming up for approval.

Is the rationale provided in the draft guidance on the use of clinical response as the primary endpoint scientifically sound? We think it's justified. It's been supported by extensive
analyses by the FNIH. We go on from there. But patients aren't yet out of the woods at day 4. Early endpoints can define failure, but we believe they should not be the definition of success, which means cure. And we're dealing with an acute disease process anyway. We're not really looking at an early surrogate for a cure because you can actually see the cure event later.

To fully conform with clinical practice and global harmonization, we recommend that the test-of-cure visit occurs at 3 to 7, or it can be 5 to 10 days after end of therapy, when relapse can occur in the absence of antibiotics in the body, with failures on day 4 onward, carried forward.

However, we don't want to be extraordinarily dogmatic about this. There is evolving regulatory science. There's evolving data that's being collected at these later endpoints. More information is going to allow us to better validate the later endpoints in ways that we will argue are robust. Therefore, we would say, if sponsor agency negotiation leads to separate analyses at the two
time points, as I said, as regulatory science evolves, only one should be powered statistically as the primary endpoint, and the other one should be consistent with and looked at carefully, but not powered because of the feasibility issues of powering both.

Question 2. Please discuss the merits and limitations of each of the pathways in trial designs. We feel all three approaches can be used, assuming that enrollment is feasible and representative of the population of interest. And this aspect of representative we think is quite important. If we're unable to do studies in the United States because of requirements that no prior antibiotics can be used, we wonder about the ability to have a representative population that will then be used to extrapolate to effectiveness in the United States.

So some specific points to consider, should the micro-ITT population be a primary analysis endpoint? We indicated earlier that we believe it's the ITT or clinical eval population from each
of two phase 3 trials that should be the primary endpoint. And we agreed that the pooled micro-ITT from two of these trials should be a secondary endpoint whose results are consistent with the primary, remembering that at present state of the art, we're only able to identify about one-third of the patients within the populations, and it's going to be very difficult to enroll enough patients to drive a powered study. Results from the micro-ITT data should be consistent across the two trials.

What is the role of serologic and other diagnostic tools? And this gets us into question 3 formally, but we thought it should be discussed here as well. Sponsors should endeavor to obtain as much culture proof and microbiology as possible. We're all in agreement with the benefit of that.

We also, though, would support the notion, as stated as well earlier, non-culture-based, validated diagnostics should be permitted as supplemental tools to prove bacterial etiology, including those due to atypicals, where appropriate and informative. And, of course, as diagnostic
tests get better, we imagine that this tool will become more powerful.

What about the single phase 3 trial? Again, the focus should be on quality rather than quantity. And a lot of this is going to be discussed as well by my colleague, Bob Fromtling, tomorrow at the HABP/VABP discussion.

But we believe that a single trial could be used, as long as there's an additional phase 3 trial available for a similar-type infection due to similar-type microbes, Gram positives, for example, skin infection, and community, or rather, hospital pneumonia, in part to get adequate aggregate human safety data. This is extraordinarily important, that we have safety as well as efficacy data. We also want to validate drug efficacy in a supportive, clinical setting.

Regardless, such a single registration trial would need the totality of supporting clinical and non-clinical evidence, and this is something that we sometimes forget about in dealing with anti-infectives. Let's remember that the way anti-
infectives work is on a microbe that we can test outside of the human body. We're not talking about complex, biological pathways involving the cardiovascular system, the CNS, where off-target effects are quite common, and one can get results that are totally unpredictable in prior models. We're trying to eliminate microbes. The totality of data, therefore, includes all of those in vitro studies, but as well, human PK and tissue penetration studies. So for community pneumonia, we'd want to get ELF data, plus we want to be able to use phase 2 data.

Animal modeling of human infection with correct pathogen, pathogenesis represents the human infection the vast majority of the time; PK/PD evaluation of drug effect that mirrors the actual human exposure that we're seeing. Target organs are appropriate. For example, when one is studying community pneumonia, the long inoculation should be done via inhalation, inhalational inoculum rather than through hematogenous, if one is looking through community pneumonia; appropriate in-vitro
studies, including the potential for inhibitors, as we discovered in our daptomycin work, surfactants in the lung, and that should be ruled out as a potential inhibitor.

Other points, the proposed margins in each approach makes very good sense. The trials, though, should be powered for a single primary endpoint evaluated at a single time point. More will be discussed, as I said, by my colleague, Bob Fromtling, tomorrow.

What is the role of patient-reported outcome endpoints to measure clinical benefit? We think that this could be of great value, but to be able to validate pros, given the difficulty we have of chicken and egg in terms of the trial designs, is an inherent problem. And we recognize, then, the FNIH proposed symptoms of cough, chest pain, dyspnea, and sputum production in the extensive review of the literature.

Let's remember, antibiotics have a profound positive effect on treating pneumonia. We have now 70 plus years of history in knowing that fact, and
we should keep that in mind as we go forward.

Safety of research subjects in the context of best clinical practice is also key, if not our first priority.

What about question 3, other issues, the severity assessment? We think that, actually, age rather than more complex systems should be used, not because those other systems aren't more informative, potentially, but to enable speed of enrollment, feasibility, we think that the simple cutoff in the emergency room would enable quicker enrollment and would get us most of the information that we need anyway.

This essentially goes along with what is presently in the draft guidance, so we fully support that, and we also think that we need to get patients below the age of 50 just to ensure that we have representative population.

What about the issue of prior therapy? In some ways, this is the most important part of my presentation because it gets to the issue of feasibility. Should we allow prior concomitant
antimicrobials? We think that these are actually
two separate issues. We agree totally, concomitant
antibiotics should not be allowed if they have an
active, activity against the pathogen of interest.

The bigger issue, of course, is the one
about priors. Long-acting priors can have a major
effect on outcome. These should be avoided to get
the most informative trial design, but prior
antibiotics are incredibly hard to avoid in
pneumonia because of everything we've just heard
over the last hour or two of discussion.

Complete forbiddance of prior antibiotics,
short-acting as well as long-acting, as an
exclusion criterion could therefore lead to a trial
on feasibility, particularly in the United States.
And if you do so, if you try to reach perfection
from the scientific standpoint by eliminating all
prior antibiotics, you end up then shifting the
focus of your studies out of the United States, and
then you run into another issue, and that is the
representation, the ability to represent the
patients, that you're looking from different

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practice situations to the United States, and that becomes a separate issue. This is why we have a very tricky issue with balance that needs to be considered.

So let me, then, in just the next five minutes or so, review in a little bit more depth the lessons that we've learned from the daptomycin for pneumonia trial. I joined Cubist nine years ago. I joined just as the results from the pneumonia trial were becoming revealed to me and my colleagues. And we were able to determine unequivocally that daptomycin was inferior to ceftriaxone. This is on the basis of two trials, the second of which was actually stopped midstream because of the results on the first one.

Interestingly, and to note mortality, while showing a trend towards inferiority, daptomycin, actually did not make inferiority statistically. So, again, it argues why mortality alone as the endpoint is probably not the best.

Also, the other point to make is this was based on the more traditional end-of-therapy
endpoint, taking into account all the criteria that we typically use for these sorts of trials, and the assay sensitivity was not unreasonable.

But we should also mention that daptomycin, we believe, is not a placebo. This difference represents the minimal effect in some points about daptomycin. We know the pathogens are extraordinarily susceptible in vitro. The antibiotic actually did work well in some prior animal models, those that involved necrotizing disease. It also worked extremely well on a hematogenous lung infection model, as well as right-sided endocarditis, where we actually had infection of the lung in our staph aureus bacteremia trial.

Daptomycin worked extremely well in these settings. It was found to be inactivated by surfactant, which became more apparent in the refined animal models that we later used, that did not deal with necrosis, and it was only then that we were able to see the difference.

So two key lessons: the inferiority
difference is a minimal effect size. The late
test-of-cure endpoints actually function very well.
Mortality did not demonstrate statistically
significant inferiority.

Of equal note, patients treated in the
United States and western Europe with daptomycin
succeeded almost as often as those treated with the
comparator. We later discovered that over
60 percent of patients treated in the United States
and western Europe had prior antibiotics.

This study was done over 10 years ago,
before the 4-hour rule came into place, and before
there was a shift, an even stronger shift, to
giving more prior antibiotics. In contrast, the
rest of the world -- over 80 to 90 percent of the
patients in the rest of the world did not have
prior effective antibiotics. So, again, we get the
discrepancy of what part of the world we're
actually looking at.

So further analysis showed the results of
these patients were confounded by the high rate of
treatment with prior antibiotics, even though they
were limited to less than 24 hours, unless the patient had failed prior therapy.

This effect was, though, limited to patients treated with long-acting but not short-acting, and I'll show you the data shortly. The draft guidance, we think, overcompensates. It says that all antibiotics should be eliminated from prior use. We think the lesson is overlearned, and it did not discriminate between long- and short-acting. And, again, we feel that to eliminate all prior antibiotics will virtually eliminate the United States from future enrollment.

So let's go through some of the data. This was published by Pertel, et al., CID. As I pointed out earlier, the actual citation is down here. So long-acting as defined by Pertel. And there's a caveat here. As we are working with the FDA to re-explore these datasets, we are finding that there may be some additional refinement of what we mean by long-acting and short-acting. But I am limiting my attention here to what was actually published in Pertel and the definitions that Pertel
used in that paper from three years ago.

So if the patient had long-acting, notice that the inferiority of daptomycin was obliterated. This is the key lesson that says we should not have these antibiotics. If you do not have these antibiotics, you get a significant inferiority. But what's often forgotten is that Pertel lumped into this analysis short-acting along with no prior antibiotics, and the short-acting included other betalactams, tetracycline, trim sulfa, and some others.

Now, the cure differences, with no prior and only short-acting, broken down here, were actually very similar. So this was none, and this was the short-acting. Now, we recognize that we're getting to a smaller number of patients, so this is, again, a subset of a subset, with all the caveats that are involved. So I just want to be clear.

I'm not saying this is definitive proof, but it is, at least, we think, suggestive, that short-acting, under certain circumstances, will not obliterate the inferiority effect that's actually
in place by the inferior antibiotic that's being used.

Then, when we further break that down into those that got less than 24 hours and those that had short-acting but greater than 24, but they failed, they had failed prior therapy, we find that, again, the inferiority is maintained, albeit with smaller populations. So that is the caveat.

So we would say, should the use of prior antibiotics be permitted in clinical trials of community-acquired pneumonia? We agree. There's no perfect solution. We acknowledge that prior antibiotics might confound the effects of the study drug, and the comparator, and thereby diminish assay sensitivity to drug effect. And, again, Tom File did a great job in reviewing some of his own data with ceftaroline, and it's shown here just for cross-reference. But delaying treatment is not feasible, according to modern practice guidelines, as Dr. File himself indicated.

So is there a way out? And we would suggest the following. Yes. If you allow prior
antibiotics, limit them, though, to brief courses of short-acting, allowing the minimal dose since there was no rescue effect, at least according to the Pertel study, to enable U.S. and European enrollment, providing the FDA with the most representative population sample of patients treated according to the best U.S. and E.U. standards. They should be permitted and recorded as baseline study information.

Such information by subgroup should be reviewed for qualitative success results, but not for statistical confirmation. It is not feasible to power these subgroups for such analysis. And another lesson I think we can learn is allow enrollment of patients judged to have been failing prior to greater than 24 hours because we, again, still preserve, if you will, the inferiority effect, at least from our study, albeit with a very small number of patients here. So this is a carefully drawn conclusion.

Some other comments that I'll just mention briefly -- there's a lot of information here -- and
I won't go through this in detail. But there's also the feeling that recent regulatory guidances have not incorporated all the data when it comes to breakpoints, microbiologic breakpoints. That includes surveillance, clinical, and PK/PD data to set this.

We would just briefly say that if you look at the MIC90, by definition, you're not going to be able to have very many patients at the top end of the population distribution. So to arbitrarily cut the break point significantly short of that because of the lack of those patients, in a way is doing something that makes it very difficult for clinical microlabs, given that they often have a 1- to 2-tube error on any given patient anyway, and also, sometimes flies in the face of PK/PD evaluation in carefully done animal models. So we think that more of this should be used in setting the breakpoints.

We also think that atypical pathogens should be included if the test drug that's being evaluated does have potency against those. We've already
heard that there is known effects of antibiotics on these pathogens. We've seen it with tigecycline. There have also been a number of well-published studies to show that there is a clear-cut placebo-controlled benefit of using antibiotics that have activity against those organisms in clinical settings.

So we feel, in summary, then -- let's not let the perfect be the enemy of the very good -- clinical trials should be feasible to do in the United States and relevant to United States clinical practice. Unlike other therapeutic areas, antimicrobials are depreciating assets. Resistance emerges steadily. Antibiotic stewardship can delay but cannot prevent resistance.

Individual antibiotics become obsolete. We must, therefore, have a continuous new supply of replacement antimicrobials. We feel the greater danger is that we err on the side of two few new antibiotics approved in the United States rather than too many. And the point here, too, is the possibility that we start to see approval of
antibiotics in other countries, but not the United States, and I think that would be not beneficial to our patients.

Finally, continued delay decreases the likelihood that our patients will have effective new medicines when needed. We seek ethical, informative, and feasible trials. Refinement is the next challenge.

Just to recapitulate the points I've made, clinical endpoints capture the antibiotic benefit. ITT should be the primary endpoint or, perhaps, CE. Use pool micro-ITT as a secondary endpoint, including non-culture-based diagnostics. Allow a single phase 3 trial under circumstances where the totality and quality of the data is strong.

Age rather than PORT scores should be used. Allow less than 24 hours of prior short-acting antibiotics, rational evaluation of susceptibility breakpoints, and permit enrollment of patients with atypicals. Thank you.

DR. MOORE: Thank you, Dr. Eisenstein.

Let's move on now to Dr. Zuckerman.
DR. ZUCKERMAN: Thank you very much. I'm Dr. Diana Zuckerman. I'm president of the National Research Center for Women and Families, which is a non-profit think tank that uses research to bridge the gap between research and health policy and research and practice of medicine. And our center does not accept funding from pharmaceutical companies, so I do not have any conflicts of interest.

I'm speaking today from my perspective, both as the head of a non-profit organization, but also my training is in epidemiology and public health. I was on the faculty at Vasser and Yale and conducted multi-center trials at Harvard. And I'm also a fellow at the University of Pennsylvania Center for Bioethics.

So my perspective is both as a scientist, someone very concerned about ethics and public health, and also as someone who is really looking for ways to improve healthcare for all Americans. And I guess I need to also say that in addition to
my 94-year-old father having worked for a
pharmaceutical company his whole career, he also is
getting antibiotics every time he sneezes,
practically, at the assisted living facility where
he now is? So I also see how often particularly
elderly people are getting antibiotics, and I want
to talk about that, too.

We all know that we like new things. We
like new drugs. We like new cereals. And this one
is Trix, and it has a new shape. So every time we
try to sell a product, we like to talk about how
new it is, and just go to the grocery store, and
see how often "new" is somewhere on packaging. But
just because something is new doesn't mean it's
better or even that it's good for us.

The importance of study design really can't
be underestimated. A good study design will save
lives. So one of the big issues that concerns us
is how often drugs of all types, and antibiotics in
particular, are studied on relatively healthy
patients. But so often these drugs are going to be
used on elderly patients who are taking many
different kinds of medication and patients who are seriously ill. And so it's very important that the studies be of the same kind of people who are, for the most part, going to be taking those drugs; just to give the example of tigecycline, which was approved and now there's a warning where FDA is reminding healthcare professionals of an increased mortality risk associated with it, compared to other drugs used to treat a variety of serious infections because it was not tested on those serious infections.

Other study design issues, as was just mentioned, allowing prior antibiotics in trials. I think that there's some agreement that doing so can help make drugs appear more similar than they really are. With all due respect, it may not be easy to do these kinds of studies in the United States, but it absolutely is feasible if the motivation is there. People can be studied at emergency rooms, for example, or certain physicians can be selected to do such studies. If it's important to do it right, it should be done right.
And if we can get clear, absolutely conclusive evidence that prior antibiotic use does not affect the results, that's one thing, but we're not at that point.

Clearly, a very important part of these studies is to confirm that the person has the disease that you think that you are studying, whether it's pneumonia or whatever it is, so kind of an Ethics 101. Do not expose people to an experimental drug if they don't have the disease for which that drug is intended. If some of the patients don't have the disease, then drugs that are inferior will look non-inferior because allergic diseases and heart failure can look like pneumonia. So we really do need to be very careful to make sure that the people in the studies -- I mean, you can exclude them later if you find out that they did not have the disease if it takes time to confirm the disease. But it's really important that the study design focus on the people with the disease.
I want to talk a little bit about outcome measures. The studies should focus on the patient's health and recovery, not unimportant signs. Signs and symptoms can be unimportant or important, depending on the person and depending on what's going on. But we really need to have a better sense of not just whether signs and symptoms are abating, but whether the person is actually getting better.

The effects of antibiotics tend to occur early, so the primary outcome should be measured early. And just focusing primarily on longer outcome time will make drugs appear more similar because some people are going to get better anyway, partly because some people aren't going to have the disease that you thought they might have.

I want to use just a couple of examples. This was in the FDA's materials that they provided. This is a very old study from 1940, but it shows the rates of clinical recovery from acute bacterial pneumonia, and you can see that in terms of recovery, the difference between placebo, which is
the red, and treatment, which is the blue, it's not that big. It's 69 percent versus 79 percent. And, sure, if you're in that 10 percent, it matters to you, and I'm not saying it doesn't. But with so many people getting better and having symptom abatements -- this is up to 72 hours, by the way, so this is short term. But with so many people feeling better, clearly, you're going to have a lot of drugs that look pretty similar to that. Placebo is doing really well.

So for that reason, I think it's really very important that we be very strict in the kind of research that we're doing. Otherwise, we're going to end up with a lot of drugs potentially looking pretty much like that placebo or a tiny bit better.

I wanted to use this other example. This was from a study that was presented over the summer at an FDA meeting on antibiotics. That was for otitis media, and I understand that's the difference. But, again, if you look at children with symptoms and you -- this is the study day through seven days. There's not much difference
between placebo and treatment. And yet, when this was discussed at the FDA meeting a few months ago, people were saying, well, there are some significant differences there. But it depends on the day, and we don't even know what's going on after seven days.

So I'm just using this as another example, that even placebo -- and I understand, this is otitis media; it's not pneumonia. But if you compare it to the other, this is going in the opposite direction because it's rate of recovery. This is going down because it's symptom relief, but it's the same finding, that placebo is doing, really, very well, and not much different, and not significantly different in many respects.

This is a PowerPoint presentation, so I'm calling these myths. I think probably a more precise definition would be unsupported general statements, or mantras, that I've heard at many of these meetings, so I just want to go over them. I have six of them.

Number 1, our animal models are so good that
we don't have to worry about doing studies in people. But according to a Tufts study, only 28 percent of antibiotics are approved. The other 72 percent all had promising animal studies, but ended up not being approved because they were not effective in humans.

Number 2, test tube results are good enough. I completely disagree with that one. First of all, test tube results can't tell you anything about side effects and safety for humans. And also, again, most antibiotics are not approved. And yet, to have gotten to that point of submission to FDA, they would have had to all look great in a test tube to get to the IND stage.

Number 3, current trial designs work well, so "If it ain't broke, don't fix it." I just want to say non-inferiority trials done today, many of them violate basic standards of clinical trials. They do not follow FDA's own regulations for "adequate and well-controlled studies." And, again, to counter that statement about current trials being fine, I think we can just look at

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Ketek and tigecycline just to show how drugs that look good in certain kinds of studies end up causing serious problems with patients.

Number 4, antibiotics are different, have to be studied differently because they attack bacteria instead of binding to a human receptor. As an epidemiologist public health person, I would just say, if the goal of medication is to prolong life and improve function or to reduce symptoms, it doesn't matter what the mechanism of action is or how the drug gets you there. What matters is what's happening to human patients. And that can be studied in similar ways with very different kinds of drugs.

This one just happened to have been mentioned in the previous presentation. I think you won't think he gave me that information ahead of time. Don't let the perfect be the enemy of the good. I don't know how many times I've heard that in politics and in public health. And that is true. We shouldn't let the perfect be the enemy of the good or of the very good, but it is not good,
or particularly not very good when people are dying unnecessarily from the side effects of antibiotics that are not as safe and not as effective as other available antibiotics. And, of course, sometimes they're dying unnecessarily because it doesn't work as well, sometimes from side effects; and particularly I would say, people who have multiple health issues, particularly elderly people, for whom these drugs have not been adequately tested.

Then my last one, it can't hurt to take an antibiotic unnecessarily. This is certainly the way many patients feel. Maybe I have a bacterial infection. Maybe it's a virus. I don't know. But it doesn't do any harm to just take an antibiotic, and it'll work or it won't work, but it won't do any harm. But we know that it does harm.

First of all, there's antibiotic resistance, which has to be a terrible problem. I see what happens with, as I said, just in the assisted living facility that I'm very familiar with, where the doctors there give antibiotics to people over 70 for everything to make sure that they're going
to be okay. They're just taking not just any antibiotics; they're taking the newest, most expensive antibiotics, which often have serious side effects for elderly and fragile people.

In addition to that, I'm sure you've noticed there's new research suggesting that altering the normal bacterial flora in the human body can cause long-term harm. We're not exactly sure what. Certainly, there are allergies and other issues that seem to be associated with that.

So we shouldn't assume it does no harm to take an unnecessary antibiotic, and that's why we need to test them to make sure they're being tested to work on patients with the disease, in this case pneumonia.

I want to just talk a little bit about hype. Hype sells antibiotics that are often more expensive but not as safe as older antibiotics. And I see that all the time, and not just with my elderly parents, but also when I go to my dentist, who is always suggesting some kind of antibiotic for something or another pertaining to my gums.
Actually, now, I have a hip replacement for a year, and so now, every time I go to the dentist, I'm given antibiotics. And maybe that's a good thing. I hope that it is. I do actually take them, but I'm always wondering what the data is to support my taking four antibiotic pills.

Research should focus on outcomes that matter. The research should compare new antibiotics to placebo in situations where that's ethical and possible or to existing drugs, but they should also be tested on appropriate patients to see if they're truly a good alternative to existing treatments for the patients that are going to be using these drugs.

Research or hype. Again, I just want to say that studies should compare different lengths of treatment. We should see whether five days is enough, or whether you really need seven days of an antibiotic. You should check and carefully study the effectiveness to determine both the impact on relief of the particular disease, but also any impact that might be on recurrence.
You should compare short-term results of these treatments, and you should also compare long-term results. You should do both. And you shouldn't replace one with the other. You shouldn't replace long-term to replace short-term, and you shouldn't pool them together. You should look at them separately and make sure they're both true.

For FDA approval, generally and specifically to antibiotics, we all know they're studied on, perhaps, a few thousand people, but then they're used by millions of people, and we need to make sure they're being studied on the kinds of people who will take them.

They're approved for one use and then they're widely used off label with very few warnings. We need to do a better job about that.

We understand that risks are inevitable for every medication. That is the price of admission. We have those risks, but we need to reduce those risks. And one way to do it is by comparing antibiotics in unbiased studies of the patients who
will actually be using them. And then just to say, needless to say, even a small risk doesn't feel small if you or your loved one is the one that's being harmed.

So, in conclusion, non-inferiority studies as currently conducted often don't protect patients from less effective and less safe antibiotics. But, clearly, some non-inferiority trials are better than others. And if we're going to be using non-inferiority trials, we should use the ones that are as good as they possibly can be.

Second point; risks are real, and labels and advertising to doctors need to be clearer about what those risks are. And then, unfortunately, three, don't expect doctors or patients to read the fine print or to actually read the study. So that's why those labels and the ads have to be very, very carefully monitored.

That's it for me, and I'm happy to answer any questions.

DR. MOORE: Thank you very much. Again, we'll have clarifying questions for all of the
speakers at the end of this session, which will follow Dr. Bartlett and Dr. Laessig's presentations.

So Dr. Bartlett, if you are ready, we will have your presentation.

**Guest Speaker Presentation - John Bartlett**

DR. BARTLETT: Hi and thank you. I'm glad to be here and talk about one of my favorite topics, community-acquired pneumonia. I preface my remarks by saying if I had an artificial hip, I wouldn't take antibiotics. If I had community-acquired pneumonia, I would sue the doctor that didn't give me antibiotics. But let me get on with the show.

[Laughter.]

DR. BARTLETT: I know a lot of people have presented a lot of information, so I was trying to not be redundant. So I hope that we have trials that will permit substantial entry of patients from the United States because we're approving it for the United States, and the United States has unique microbiology and care standards.
Pre-randomization of microbiology is just not possible. It's just not possible. You talk to anybody that works in an emergency room and say you've got to enroll a patient with community-acquired pneumonia within the six hours of their time of registration, they're going to say, "We can't do it." We just can't do it. It's never been done. It's not going to be done. There's no pathogen identified in 80 to 90 percent of the cases for reasons that are a bit enigmatic, but nevertheless a reality that we have to face.

As I mentioned, you have to start antibiotics within six hours, and that's a rule. And it's a rule that has applied. It's going to apply with healthcare reform. It's going to be monitored. And the reason it's a rule is because mortality is significantly different, worse, if you wait more than six hours. And that's on the basis of a very robust database from Medicare, from 12,000 patients.

That means that you're really going to have to have some short-acting antibiotic in order to do
a trial in the United States. I would have trouble doing it in another country, knowing the waiting longer is going to harm patients.

Randomization should simulate practice, and practice is empiric. I mean, you have pneumonia. We give you this drug on the basis of these data. We have guidelines for how to treat pneumococcal pneumonia, Legionnaire's disease, and so forth, but the frequency with which they apply and can be used is not very often.

The clinical response, the signs and symptoms at 3 to 5 days makes sense to me on the basis of historical data, which I'll present in a minute, and 3 to 17 days, which has been suggested, and I think it's reasonable. The response can be objective and subjective, and I think the patient-recorded outcome is probably a good idea, although I don't know quite how it's done.

Microbiology, we've got to be able to get good tests. And we're at the dawn of a revolution in diagnostic testing. So, for goodness's sakes, let us test the new test while we're doing
pneumonia, but not make the test part of the enrollment criteria.

So here's the historical data. And I listed some of the authors, but actually, the meta-analysis is probably the most important. It's on the basis of 67,000 cases of pneumonia, and the mortality rate was about 35 or 36 percent. For the studies in the United States, it was 19,000 patients and 33 percent. So mortality of community-acquired pneumonia is pretty well-established in the pre-antibiotic area.

Now, in terms of what are the bad risks that predict death, I was a little bit surprised by this. I had to pick from the various studies that analyzed for the variable I'm looking at. But white count turned out to not be a very good predictor. It was only significant when it was less than 10,000. It wasn't even significant when it was more than 60,000. Fever got significant when it was above 106.

[Laughter.]

DR. BARTLETT: And respiratory rate got
significant when it was more than 50.

The thing that really stuck was age. Age is an important variable. And here are some data from Mass General back in the 1918 era. And what they showed was that the very young and the very old are the ones that are most at risk, and is sort of reminiscent of what Barry Eisenstein said.

The natural history, the acute course is 5 to 10 days and 70 percent. If you want the mean for all those studies with 16,000 patients, it's about 5.8 to 7.9 days, and then it's rarely less than four days, but I can't put a number on that.

The time that the patient is actually better, in other words back to baseline, is about 20 days. And the time the x-ray is resolved, that is, the infiltrate is cleared, is a mean of 20 days with a fair amount of variation.

So based on the analysis of 10,000 to 20,000 cases, the mortality is 33 percent. The acute illness is about seven days, and that's when they defervesce as an average. They get better enough to build back to baseline in 20 days, and the x-ray
is cleared in that time.

Now, I want to mention something about microbiology because I think this is a great opportunity for us to combine studies where there's an enormous amount of clinical data collected and can study some of the new diagnostics. And we've got to move off of the period in which we are doing microbiology based on the techniques developed 160 years ago. We've got to move forward.

So in contemporary practice, the diagnostic yield is 7 to 8 percent. In the FOCUS trials, they were better, 15 to 25 percent, but half of that is atypicals and half of that is the pneumococcus or the staph aureus. And the techniques, as I mentioned, that are currently available are Gram stain and culture, are things that Louie Pasteur did in 1850. I mean, that's what he did. Well, he didn't do the Gram stain. That came from Hans Gram in 1890.

Urinary antigens and molecular tests are currently available for respiratory viruses, but are not FDA-cleared for any bacteria that I know of.
that cause pneumonia.

So there are multiple new methods that could revolutionize our ability to identify the etiologicication of pneumonia and a lot of other anatomical site infections at other anatomical sites as well.

What we really want are things that are rapid, including CLIA-waived point-of-care tests that satisfy the assured criteria. That is, they're cheap, they're sensitive, specific, user-friendly. It means they don't require any training to speak of. They're rapid within 20 minutes or an hour, the time somebody's in an office or an emergency room, and don't require equipment. In other words, they don't require a lab, and you can do them in the emergency room or in the office.

Now, the way we do it now is based on the data that were largely developed by John Washington and then modified a bit by Geckler. And then here is interesting information that is applied to this by these authors, which say that if you have the satisfactory cytologic criteria, and you can see
the pneumococcus with more than eight organisms per oil immersion field, it's pneumococcal pneumonia.

These are data that I thought were interesting in terms of what Don Craven will talk about tomorrow, and that is quantitation. When we quantitate the bacteria and sputum, for pathogens, the mean is 10 to the 6.6. And when you translate that using John Washington's criteria, that means you've got five colonies in the third streak.

I don't think very many people actually use that, but I think it was kind of interesting to have probably the great leader in the field of sputum bacteriology, John Washington, identify five colonies in the third streak.

So microbiology. Well, microbiology by Bullowa, who was very aggressive in getting the specimen, was 98 percent. He identifies the pathogen. At the present time, we get a pathogen 7.6 percent of the time on the basis of the Medicare experience with 17,000 patients. So we really don't identify the cause of pneumonia, which is bad medicine for most of us. It's not the
physician's fault. I mean, we can't do it. Even in studies, when you struggle, with everything we currently have, it's been a problem to identify the etiologic agent of pneumonia. And we're hoping that the molecular techniques might provide the light at the end of the tunnel with identifying the cause.

So here's kind of a history of it. It goes back for the pneumococcus. It's only about the pneumococcus. But 81 percent, and then you can see that as you go through the years, the yield of the pneumococcus goes down, down, down, down, down, and we don't really know why.

So in the FOCUS study, where they worked hard -- and Tom File is here and one of the two lead authors on these papers that showed the pneumococcus in about 10 percent, staph aureus in about 4 percent, and atypicals in 12 percent. Well, that's better than average, and it's using the diagnostic techniques that are currently available.

Now, we do have virology tests that can be
detected with molecular techniques, and these are
the sensitivity and specificity for various
respiratory tract viruses.

Now, on the panel from film array are
atypicals. So we could probably get that
information for all three atypical agents, but
they're not FDA-cleared yet, and the hope is that,
maybe, if we do the right studies, we'll be able to
do it.

Now, there's a host of trials using
molecular techniques to identify chlamydial
pneumoniae, but they can't find any. So they wind
up with a huge number of negatives and not enough
positives to be able to cross the goal line with
regard to clearance. They also identify the
pneumococcus, but, you know, if you would get the
pneumococcus out of expectorated sputum, you can't
tell whether that's a colonizer or a pathogen. So
you've got to somehow do a quantitation, get a
quantitation, or a semi-quantitation evaluation.

In fact, this is what they do at the
Karolinska Institutet in Sweden. They do
quantitative microbiology. So their pneumococcus
and their H flu, for example, are called positive
if they have more than 10 to the 6th per
milliliter. That's their threshold. And it's sort
of reminiscent with what I said before. That means
identification of the organism by itself, or
organisms that are commonly colonized, is not going
to be adequate to identify the cause of the
pneumonia.

Now, there are other tests like this fish
analogy, which is a molecular test that looks at a
Gram stain. And it's semi-quantitative. The
results are available in 20 minutes, and it costs
$30. This is before European authorities now, and
it will come to the United States. So there is the
promise that we'll be able to do this, maybe even
do it in the emergency room.

Then this is kind of the Cadillac. This is
the T5000, the old IBIS 5000 machine, that finds
everything. And it actually is credited with
identifying 2009 pandemic, H1N1. And this will
certainly identify everything that can be
identified in the way of a microbe, except parasites. So it detects bacteria viruses and fungi. It takes eight hours, but it's going to go down to three hours. It's quantitative. It tells you how many are there. And it costs about $80 a sample, or that's the expectation.

Now, I feel strongly that we really need point-of-care tests because most of the emergency rooms in the United States and the offices are very distant from the laboratory that's going to serve them. And anybody that's in practice knows that if you're going to collect a specimen, a sputum sample, in the emergency room or in an office, it's going to be a long time before you get a reading in most places.

So at Hopkins we have the hospital laboratory in the same facility, but it's a half-mile walk. What I want is one that can be done in the emergency room, and that means CLIA-waived. So they're doing this in England, and this is their results with point-of-care urinary antigen tests. And they had compared to having an untrained nurse
read it instead of the laboratory technician,  
98 percent concordance, and they got the results in  
time to influence decisions about antibiotics. But  
if the lab did it, it took a day. And that  
patient, of course, is already being treated and  
either home or in the hospital at that point in  
time.  

So my message with regard to microbiology is  
that the current methods are delayed, the yield is  
low, and the reason for difference with historic  
data is unclear. But what we really need are tests  
that are rapid, specific, and I put in parenthesis,  
sensitive. What they really need to be is  
specific, because if I've got, for example, the  
pneumococcus, I have to make sure, or would like to  
make sure, that that's the pathogen for the reasons  
that I mentioned. Therefore, sensitive is not as  
important to me as being specific.  

It ought to be CLIA-waived. And I think the  
promise is with molecular tests, and we're all very  
interested in procalcitonin and its role in  
deciding when to start antibiotics and when to stop
Now, in terms of the IDSA/ATS guidelines, what I did was to list what they are, and then I put the quality of the evidence that supports them in this little superscript here. And that's the quality of the evidence, which means it survived a controlled trial.

So these are the guidelines. I'm not going to belabor the stuff; it's on the screen. But I would only say that this is a well-oiled machine in terms of the group that does it, who are acknowledged authorities in the field, and their ability to respond to new information. And now, they're in the process of rewriting, or will be soon rewriting these guidelines.

As far as I know, everyone who has reviewed the guidelines, applied the guidelines and critically analyzed outcome has said that they work. When they've been compared to ad lib recommendations for antibiotics, they have been better, in general.

Now, they also say that when the patient is
better, they should go from IV to PO, and they're very specific in terms of the criteria to do that. And the only reason I mention it is, when a patient goes from IV to PO, they're one step toward the door; they're going to be discharged. And that's very important, to get people out of the hospital.

My reason to emphasize it here is, I really think that clinical trials have to simulate practice, especially when it comes to the potential harm to patients by participating in a study. So we keep them in the hospital too long, they're subject to possible harm, especially if they're getting an IV, and you all know that. And, therefore, I would emphasize the fact that we really ought to try to simulate those guidelines that I mentioned as much as possible.

The duration of antibiotics is stopped when the patient's -- this is the IV -- when they're afebrile for 48 to 72 hours, the antibiotic has been given at least five days, and there are no complications in terms of vital signs, oxygenation, and mental status.
Severity scoring, we can argue about the PSI, or the CURB-65, or age, or whatever. I don't feel strongly about any of those.

The data I mentioned from Medicare I think are robust in terms of numbers, not perfect in terms of science. This is a retrospective analysis. It's a comparison of ceftriaxone to cefotaxime as the basis for the evaluation of all other combinations, the ones that seem to make a difference as the cephalosporin plus a macrolide, or a fluoroquinolone alone.

This has been a bit of an enigma because it's uncertain if this has to do with the anti-inflammatory effect of the macrolide or if it has to do with their activity against atypicals. But one way or another, it does seem to make a difference when you add a macrolide. Even with pneumococcal pneumonia and bacteremia, when you add the macrolide, it seems to make a difference, even though you know the workhorse and the gold standard is penicillin.

This is the global experience with
community-acquired pneumonia for atypicals, and this is the frequency. They have positive serology. I'm not going to talk about serology. I personally am not a believer in serology, but I'm not going to make that argument here for atypicals. It would do for Legionella, but not the others, but this is not the time for that debate.

What is interesting is the national standard for empiric use of antibiotics in terms of coverage of the atypicals is very different in different parts of the world. And that's part of the nationalistic differences that I mentioned at the very beginning.

I also wanted to mention the potential concern about the increasing resistance of the pneumococcus. And this may be a byproduct of the use of the Prevnar 7 vaccine. And it probably is, with the emergency of the 19A strain. In other words, it's kind of a moving target. We're still under the wire, the threshold for penicillin. But nevertheless, I think it's worrisome in terms of a trend. And all I'm saying is that this may differ
a great deal, depending on the use of the vaccine.
And, therefore, that's probably a consideration if
you're going to say that the pneumococcus is your
number one target, and it usually is.

This is macrolide sensitivity for the United
States. And this is 50 percent here. So you see
there's a bunch of the area of the United States,
and that is pretty high, macrolide-resistance.
This is by the pneumococcus, by the way.

Then as you work out toward west -- so, in
other words, location does matter. In the world,
it's hugely different. So in the United States,
it's 41 percent for the pneumococcus being
resistant to macrolides. On the other hand, in
England, it's down to 7 percent.

So these are the issues that I've talked
about. The clinical presentation is very well
standardized. I mean, we know when people have
community-acquired pneumonia. There will be a few
cases where people equivocate about whether it's
congestive heart failure, or a pulmonary embolus,
or something. That vagary has been well worked out
in studies that have been done by Dale Bratzler and others. It doesn't happen often, but, nevertheless, it is a concern, just as was mentioned, but it's not a common problem. By and large, community-acquired pneumonia is pretty straightforward, clinically.

In the pre-antibiotic era, the pathogen was recovered in 98 percent. In the current era, it's very low. The natural history of mortality is 33 percent. The current era for hospitalized patients, not walking pneumonia, which is about 75 percent of people that have pneumonia -- 7 percent that are hospitalized die. And the time to be afebrile for the pre-antibiotic era is seven days, and in the current era, it's less than 72 hours, but I couldn't get a specific number.

Practical application. Well, CAP trials really should have substantial entry from the United States for the reasons I've mentioned. I think the NIAID network that's going to be started in 2014 is inviting for the kind of study that we would like to do, but it's unlikely, and the reason
is because it's underfunded. It's going to be
10 [million] to $20 million, and the competition is
huge. I mean, they're supposed to study
resistance. And it's infection control, and it's
antibiotics trials, and it's bug exams, and so
forth. So I don't think this is going to get us
out of the dilemma of having United States
participation.

Pre-treatment microbiology with results is
just not going to happen, not unless we start to
get some molecular tests that are not available
now. The comparator ought to go by the IDSA/ATS
guidelines because that's standard of care, and
everybody marches to that drummer, and they have
to. And in the future, under the new rules for the
Obama healthcare plan, it's going to be 99.6
compliance. So those are marching orders in the
United States. The requirement, therefore, is
going to require pre-randomization antibiotics,
short-acting, preferably. And evaluation, I've
talked about.

Biomarkers, it would be lovely to have
procalcitonin throw in, to know what it would help. And, of course, many of us just do not understand why we have to do trials in Europe, and trials for their authorities, and trials for the United States' authorities, asking the same question of safety and efficacy. And, yes, they have to do it twice. We're asking the same questions, often have the same patients. It continues to bother us, but I don't think this is the point to debate that. Thank you.

DR. MOORE: Thank you, Dr. Bartlett.

Dr. Bartlett, I owe you an apology. Although your first slide indicated that you were representing IDSA, I failed to say for the record that Dr. Bartlett was invited to represent the Infectious Diseases Society of America. It's a little late. Sorry about that.

DR. BARTLETT: I should also mention, I don't have any conflicts.

DR. MOORE: Thank you. Thank you again, Dr. Bartlett.

Let's move on, then, to Dr. Laessig from the
FDA Presentation – Katie Laessig

DR. LAESSIG: Thanks, Dr. Moore, and good morning. And I'd like to thank the speakers who preceded me for their excellent and thoughtful presentations. So I've been tasked with presenting some possibilities for the path forward for CABP drug development, so I ask that you please not shoot the messenger.

[Laughter.]

DR. LAESSIG: The outline of my talk, I'll cover the proposed study population and comparators, which are straight out of the draft guidance. Then, as if you haven't heard it enough already, I'll talk about prior anti-bacterial drug use, as well as concomitant medications, and then move to the proposed development options and the issues for the discussion this afternoon by the committee.

So the study population is targeted to identify subjects who actually have the disease of interest. So we are recommending at least two of
the following symptoms, which include difficulty breathing, cough, production of purulent sputum, chest pain, and plus or minus chills, rigorous feverishness, decreased or absent appetite, and new limitations in activities of daily living, as well as at least two abnormal vital signs, which may be fever greater than 38 degrees Celsius or a hypothermia less than 35 degrees Celsius, hypotension with a systolic blood pressure of less than or equal to 90 millimeters of mercury, a tachycardia with a heart rate greater than or equal to 100 beats per minute, and tachypnea with a respiratory rate greater than or equal to 24 breaths per minute, as well as at least one other clinical sign or lab finding associated with CABP, which may include hypoxemia with a Pa02 of less than 60 millimeters of mercury by ABG, arterial blood gas, or room air pulse ox of less than 90 percent.

Physical exam findings may include evidence of pulmonary consolidation with dullness on percussion, and bronchial breath sounds, and
egophony, as well as increased white blood cells, or leukopenia, or a bandemia.

In addition, we're interested in chest radiographs with evidence of new infiltrates and a lobar or multi-lobar distribution. And we request that full, final radiology reports of the pre-treatment chest x-ray and any subsequent chest x-rays be included with the case report forms.

We're interested in purulent sputum by Gram stain, as defined by less than 10 squamous epithelial cells and greater than 25 polymorphonuclear cells per low-power field. We would also like subjects to be enrolled with a greater severity of illness, and the pneumonia patient outcomes research team or CURB-65 scores may be used as approximates of severity measures.

For IV drugs, we are recommending no subjects with a PORT score of less than 2, no more than 25 percent with PORT II, and at least 25 percent with PORT IV to V. For orals, we're recommending no PORT I's and at least 50 percent PORT III. And as you've heard, this ties to the
historical evidence of sensitivity to drug effect, such that the greatest evidence was seen in older subjects greater than 50 years of age and those with bacteremia.

The point has been raised that perhaps we can just use age greater than 50 to make things a little bit simpler, but remember that an age of 50 years or greater only gets you to PORT II, and the committee would need to consider the absence of any data in younger patients.

The comparators, as has been discussed at prior meetings, placebos are not acceptable. The active comparator should be an FDA-approved anti-bacterial drug that is considered the standard of care for this indication at the recommended dose and duration, as found in treatment guidelines or in a proof product labeling.

So in case you were napping before, prior anti-bacterial drug use is really problematic because it reduces the difference between the treatment arms and makes two drugs look the same in a non-inferiority study.
Now, priors may be acceptable in the case of clinical failure, provided objective criteria are pre-specified and documented on the case report form, or in the presence of resistant organisms, where you had a prior drug that wasn't active. And we have a concern that the impact of prior antibiotics may be even more a problem when we use an earlier time point such as the one being proposed at day 3 to 5.

So, yes, the Pertel paper, everyone knows. This is Table 6, straight from the paper, where there was prior effective therapy made. The cure rates between the dapto and ceftriaxone arm look similar, whereas dapto was clearly inferior amongst the patients who did not receive prior effective therapy.

Now, some comments on the paper. As you've heard by Dr. Eisenstein, the treatment with antibiotics -- prior effective therapy was defined as treatment with antibiotics with greater potency and longer half-lives, so levofloxacin, ceftriaxone, azithromycin, and clarithromycin.
The findings were biologically plausible due to the susceptibility of strep pneumo to active anti-bacterial drugs. And, in addition, the interaction with surfactant in daptomycin, so the daptomycin was bound up and not active in the alveolar space but has been correctly pointed out it was a subgroup analysis.

Additional analyses of the short- versus long-acting anti-bacterial drugs may be informative. And Dr. Eisenstein and Cubist have kindly provided the agency with datasets, and we are attempting to replicate the findings that have been presented.

But we don't only have the information about daptomycin. We also have information from the ceftaroline approval. This is Table 19 from the statistical reviewer, Dr. Rubin's review, which is available at drugs@fda. So this is showing clinical cure rates at the test of cure, so what used to be the primary endpoint by prior antibiotic use in the modified intent-to-treat evaluable population. Now, it's broken out be these two
registrational studies, Study 08 and Study 09.

Here, you can see prior antibiotics. The point estimates look pretty much the same. The confidence interval includes zero. However, amongst the patients who did not receive prior antibiotics, ceftaroline looks better. In fact, for the study, the lower bound of the 95 percent confidence interval is above zero. For 09, again, amongst patients who got priors, it looks about the same, includes zero, no priors, point estimate in favor of ceftaroline, just barely below zero.

So we also looked at the effect on the early time point, so the symptomatology at day 3. And you can see, amongst the priors, they're pretty close on the point estimate. It includes zero. And this is obviously both studies pooled. Amongst patients who got no priors, ceftaroline actually looks better. The lower bound is above zero.

What's different about this also, compared to the daptomycin experience, was only one dose of a short-acting drug was allowed. But we don't really have a clear explanation for this finding.
However, I note Dr. File's remark regarding ceftaroline's affinity for penicillin-binding proteins with interest. And again, you're seeing that the use of the priors was masking the difference between the two arms for both the traditional endpoint at test of cure and the early endpoint.

Now, one can sort of think, well, maybe those subjects who got the priors were more ill. But in any case, it emphasizes that the priors will drive the two arms to look similar, even when they may not be. And in this subgroup analysis that wasn't pre-specified, the outcome for subjects with no prior drug use showed a numerical trend of better response with ceftaroline compared to ceftriaxone, which was similar to the overall efficacy conclusions.

So concomitants, we recommend avoiding use during the trial for other infections unless they don't have activity against target CABP bugs. Subjects who receive such therapies should be excluded from the evaluable populations and
considered failures in the micro intent-to-treat and the ITT analysis populations. Clearly, subjects who require rescue anti-bacterial therapy for CABP should be considered treatment failures and included in all populations for analysis.

So now, moving on to our proposed options, option 1 is two non-inferiority trials. The primary endpoint would be assessed between days 3 and 5 and as a symptom improvement endpoint, which includes the four components as outlined by the FNIH proposal; so no worsening of dyspnea, cough, sputum production, chest pain, and plus or minus exercise tolerance, feverishness, and chills and rigors. This assumes an 80 percent success rate in the control group.

The primary analysis populations are the intent to treat for each trial and a pooled micro-ITT across trials. And the reason for the pooled micro-ITT is because we want to know that the patients have the disease of interest.

The key secondary endpoints would include stabilization and normalization of vital signs by
day 3 to 5, which is consistent with treatment management guidelines and clinical response at end of therapy. So we certainly wouldn't have blinders on and only be looking at what happens in day 3 to 5 and not care about what happened at the end of treatment or later on. We would be looking for consistency with the primary outcome, as well as durability of the treatment effect.

The proposed margins are 10 percent for the ITT and 15 percent for the pooled micro-ITT. And we've assumed a 27 percent micro evaluable rate, and this is based on what we've seen for previous registrational trials.

So the trial sizes are 688 per trial for an 80 percent power across all primary analyses and an N of 860 for 90 percent power across all primary analyses, which gives you either a safety database that's of 688 or 860 at the to-be-marketed dose and duration, in addition to whatever data is generated from phase 2. And this size database is likely to be reasonable, provided there are no safety signals identified that need to be further elucidated.
The second option has a slight twist to it in that it adds stabilization and normalization of vital signs to the primary endpoint. So, again, you're having the symptomatology, but now, you're also having stabilization and normalization of vital signs. And, again, this has basis in treatment and management guidelines. So this assumes an 80 percent success rate on the symptoms and a 70 percent success rate on signs. The primary analysis populations are ITT in each trial, again, and the pooled micro-ITT across trials.

So as with option 1, a key secondary would be the clinical response at end of therapy. Again, we would be very interested in consistency with the primary endpoint and durability of treatment response. So the proposed margins for this option are 10 percent for the ITT and 15 percent for the pooled micro-ITT, the same assumption regarding the percentage of micro evaluable patients.

So you note that sample sizes are slightly larger for this option because they're being driven up, because you only have a 70 percent success rate.
on signs. So it would be an N of 980 per trial for
80 percent power across all primary analyses and an
N of 1180 for 90 percent; similar comments about
the safety database, slightly larger because you've
having bigger studies.

So option 3 is for a single non-inferiority
trial, and this is back to the symptom-improvement-
only endpoint that would be assessed at day 5. The
primary analysis population is the micro-ITT, and
you can see the ends there for the various power
calculations and the various non-inferiority
margins.

The safety database, respectively, would be
about half of each of those trials if you're using
a one-to-one randomization plus the phase 2 data.
So you couldn't come in the door with just one
study on its own. You would have to have
supportive information. This might include a
successful HAP/VAP trial if you have a broad
spectrum agent or one that has activity against
Gram positives. Alternatively, it could be a
successful skin trial if the drug is active against
Gram-positive bacteria.

So as Dr. Cox has already highlighted or shown you this earlier this morning, the issues for the committee's consideration this afternoon include the endpoints, symptom stabilization improvement, plus/minus the assessment of clinical stability, the non-inferiority margin justifications, acceptability of various margins, thoughts on the proposed development plans, any other ideas for trial designs, very importantly, what to do about prior receipt of anti-bacterial therapy, any methods to enrich the micro population, mechanisms to overcome barriers to trial conduct, and then lastly, any advice on trials for PO drugs.

I'd like to acknowledge all my colleagues who helped me put this presentation together.

Thank you.

Clarifying Questions to the Presenters

DR. MOORE: Thank you, Dr. Laessig.

All right. It's 11:40. What we'll do is we'll now ask for questions of the presenters.
Dr. D'Agostino?

DR. D'AGOSTINO: The presenters talked about 3 to 5 days for the clinical, and 5 to 7 for the cure, and then even up to 13, 17 days. So one of my first questions, or my first question is -- maybe it goes solely to Barry and the FDA presentation. But how does what is being presented at the very last presentation gel with the fact that it doesn't seem to be resolved in terms of 3 to 5 days versus a 5- to 7-day cure, and even a 13- to 17-day?

Are those really to be excluded, or are they still on the table for discussion?

DR. MOORE: Dr. Cox or Dr. Laessig, do you want to handle that?

DR. COX: Yes. So I think it was in Dr. Nambiar's presentation. The earlier endpoint, the day 3-to-5 endpoint is the one where we've got some historical data on effect size, looking at symptoms at this earlier time point. And as we've talked about, the pneumonia at that point in time isn't fully resolved. And we would still look at
the later time point as a key secondary endpoint to
make sure that, in fact, the patient's pneumonia
has resolved, and they don't need additional anti-
bacterial drug therapy.

So as you've heard us describe in our
presentations, we've described an early time point
look at day 3 to 5, and then also still being very
interested to see what happens with the later time
point. You've heard other presenters talk about
trying to look at a composite of those two, and
that -- I don't know. Dr. Eisenstein may want to
further comment on that.

Does that answer your question,
Dr. D'Agostino?

DR. D'AGOSTINO: Well, I hear what you're
saying. I'm still worried are we going to be
focusing, later on in the day, just on the 3 to 5,
or do we still have --

DR. COX: So we welcome comments on both the
early endpoint that we've talked about, and then,
as you've heard in other presentations, the later
endpoint, too. If there are particular thoughts or
comments you'd like to share on that, we'd certainly welcome hearing those.

DR. D'AGOSTINO: Well, maybe some of the presentations -- Barry might want to say some more words in terms --

DR. COX: Sure.

DR. D'AGOSTINO: -- why we should have it on the table.

DR. COX: It's at the chair's discretion.

DR. MOORE: Absolutely, the more information the better.

Dr. Eisenstein, if you would like to, respond to this.

DR. EISENSTEIN: There's no clear solution, given that we have the HESDE, historical evidence of sensitivity drug effect, best demonstrated at day 4. That said, as an infectious disease clinician, I feel, and most of my colleagues would feel, we want to be sure that the cure is durable and that the patients do well when antibiotic is no longer around and patients haven't relapsed.

So we're trying to come up with a way to
capture both of those, if possible, and we thought that the composite might make the most sense. We don't object, though, to the proposal put forward by the FDA of a primary and then a secondary later, as long as the secondary is not powered to demand non-inferiority attainment, because what you're then doing is giving additional opportunities for the trial to fail on chance alone, and we don't think that that's appropriate.

Nonetheless, there should be qualitative similarity in the results, and the FDA always has the prerogative to reject an application on the basis of what they consider to be out-of-bounds results.

DR. D'AGOSTINO: I have just a second part of this question. I have other questions, but I know other people are -- that's why I was only asking the second part on this.

So following up on that, what I was thinking is that you were saying power only on one in your presentation. And so if we went with the 3 to 5, because that's where their information is and so
forth, and then you talked about the 5 to 7, that
would be secondary, and the power would be on the 3
to 5 days. So it is in conformity with what we're
hearing. Thank you.

DR. MOORE: Thank you. Dr. Reller?

DR. RELLER: There's been much discussion of
whether prior antimicrobial use is a major or minor
confounder. But what I've not heard is any
discussion or mention of how that would be
ascertained. Patients have prescriptions written
and not filled. They have filled but not taken.
They have leftover antibiotics when they're sick,
to see if they get better, that they take without a
prescription.

Then, in many studies, of acute febrile
illness, at least, in different parts of the world,
if one actually measures antimicrobial activity in
urine, whether or not it's mentioned in the
history, there's antimicrobial present.

So if this is such a major issue, how do we
know whether it's really there or not?

DR. MOORE: That's an excellent point,
Dr. Reller. Yes. I think one of the major studies from the Philippines was that in studies in countries where antibiotics are freely available over the counter, that's a major confounding factor.

Dr. Goetz?

DR. GOETZ: I wanted to follow up, in a sense, on Dr. D'Agostino's question. So as a non-statistician, I wonder if the FDA or someone on the panel could comment on what the power considerations would be if failure early, defined as lack of symptom response, were carried forward to the test-of-cure point in time, rather than have a primary endpoint at the 3- to 4-day point and a secondary measure for test of cure.

I don't fully understand myself all the statistical ramifications as to what that would do to powering the study and the number of patients necessary.

DR. MOORE: Dr. Cox?

DR. COX: I'll start, but then I'll need some statistical help. I think, too, one of the
things that Dr. Goetz's question brings to bear is,
one of the reasons for looking at the earlier time
point is that that's the time point at which we're
able to understand treatment effect. And it's not
to say that there may not be treatment effect later
on; it's just that there are limitations to the
available information. So that's been one of the
things driving us to look at the earlier time
point.

As far as his question, I don't know,
Thamban, if you want to speak to that, or if Daniel
wants to talk to the issue of -- it sounds like
what you're describing, Dr. Goetz, is sort of a
variant of an endpoint that would include both
events early and events later on, and in essence
combine the two.

DR. GOETZ: Yes. Dr. Eisenstein's comments,
rightly put, about the anti-inflammatory
activities, some of our medications such as
azithromycin might give a false sense of assurance,
potentially, that patients are responding when
they're not. Late pleural-end complications, such
as empyemas, might not be picked up by that early
time point. And, thus, that leads to the
consideration of some way of carrying forward that
information.

    DR. COX: I'll let Thamban talk in just a
minute, but even in the setting where the primary
endpoint is at day 3 to 5, and that's what we're
looking at, if there are untoward events that
happen at a later point in time, those would
certainly still be important issues to look at.

    A disproportionate number of patients
developing empyema, a high number of patients
developing recurrence would certainly be a concern
and something that we would have to look at very
carefully, even though it wasn't the primary
endpoint. Much like if there were safety issues
that were to arise with a drug, in that same
fashion, we certainly do take those into
very -- very important findings and something that
we need to very seriously consider.

    Dr. Valappil?

    DR. VALAPPIL: As Dr. Cox said, we are going
to be looking at the primary endpoint after day 3 to 5 or the clinical resolution of symptoms. Understand that at that early time point, all the symptoms will not be resolved, but we will be able to see some improvement in symptoms.

So the study will be powered at day 3 to 5 for the symptom resolution; however, we will still be looking at the sustainability of that effect at a later time point or time points.

DR. MOORE: Thank you. I think we're looking primarily for reassurance that those major events wouldn't be discounted if we're just focused on the primary endpoint. It sounds like, obviously, those would be evaluated very carefully.

Dr. Fleming, did you have a comment?

DR. FLEMING: Just to respond to the question, I think in the FNIH proposal to look at day 3 to 5 on symptom resolution, it was based on the fact that it was an evidence-based justification, that if you had a non-inferiority assessment there, that you would, in fact, be able to conclude that you have clinically meaningful
benefit.

There's the sense, I think strongly felt, though, that you want to have some reassurance, for reasons that have been well-motivated, that over the long term, that you're adequately effective. And so the essential assessment that was put forward is to at least make sure, when you're looking at overall safety data, long term, clinical response, or whatever you choose to look at, that things aren't unfavorable.

The problem with the long term, for example, if we were using clinical response at test of cure, the problem is there are issues around the clarity of its definition. It's mixing biomarkers and clinical efficacy measures. And there's no evidence to show that you could set up an NI margin there.

So it wasn't proposed as a primary endpoint, but it would be an acceptable measure to use among those other assessments you look at long term, to be reassured that the efficacy you've established short term is not, in fact, lost. It's a different
world, though, if you pool them together. If you pool together a measure that's based on symptoms early and signs late, that's no longer a symptom-based measure.

So, very simply, suppose you have a standard effective therapy and an experimental therapy, and they both, in 70 percent of the population have full proper resolution of symptoms and signs? Suppose, however, that the experimental therapy in the other 30 percent doesn't provide benefit in symptoms or signs? But suppose the experimental therapy -- the standard therapy, in those other 30 percent, in half those patients does resolve symptoms, but has not full resolution of white blood counts, for example? Then, essentially, if you pool signs and symptoms, the two regimens are the same at 70 percent success and you would call the experimental therapy non-inferior. But when you're looking at symptoms, when you're looking at what directly matters to patients, you would have a 70 percent success rate in the experimental therapy and an 85 percent success rate in the standard. It
would truly be inferior.

So an agent that truly is inferior in symptoms, if you do a composite measure, could look, in fact, similar. And so the essence is, if you're going to use evidence-based non-inferiority margins and direct measures of functions, feels, survives, we aren't only going to have to look at mortality, which is what we were looking at in 2009; we can come up with non-inferiority margins based on a 4-day endpoint. And we can then look separately, not as a composite endpoint, separately, to see, long term, can we rule out that unfavorable safety risks have occurred or unfavorable efficacy has occurred long term.

So long term, we can't establish efficacy unless there's superiority, but we should, in fact, rule out that you have an unfavorable result long term, which would compromise the efficacy you would have short term. So the critical point is, yes, you do supplement the short term. You're not necessarily required to have statistical evidence, but you do look at it, but it's separate from the
assessment you're making at four days on symptoms.

I don't know if that helps answer your question.

DR. D'AGOSTINO: Tom, can I add to that?
Because I think the question that Dr. Goetz and myself were asking is the sequential, not the lumping? I think that confusion, but was raised in the presentation is that you could power on one. And what if you powered on the 5 to 7, and somehow or other, you started, then what do I do about the 3 to 5?

So I think the sequential is answering my question. You go to 3 to 5. You put your money there. That's where your power is. And you certainly look at this follow-up of 5 to 7. So I don't think that either of us are trying to lump them together and come up with this mish-mash, as you're well pointing out.

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

Dr. Rex?

DR. REX: Thanks. So to add a little bit to that, there's one point that everybody needs to
recognize. It's going to cause your brain to hurt for a second, so I apologize in advance.

The FNIH endpoint talks about symptoms being better at day 4, but note what's not in there. You can still be febrile. You can have had an adverse event. You can have been switched to another drug. So be very careful about what you're talking about in that endpoint.

Now, biologically, most people who are better at that point should not have those things. And most of the time, switching in the first two or three days is relatively uncommon. But I want to warn you what's in the endpoint.

So that's the flaw in that approach. And there have been a lot of debates within the FNIH group about how best to address that. The compromise that's been proposed is just that. It's one that balances what we can do with what we'd like to do. I think it's really tricky to recognize what's going on there.

Really, the whole thing gets down to the trade-off. Actually, the fundamental question for
today and tomorrow is the trade-off between what
we'd really like versus what we can do.

Just in case you guys missed it, there was a
really nice letter from the IDSA to FDA recently
that pointed out this question about balancing
public health risks versus benefits for the
decisions that must be made, even in the face of
incomplete or imperfect data, and apply it to the
evaluation of the safety and efficacy of new anti-
infecive drugs. So I think this theme really runs
deeply.

So there's something fundamentally very good
about this 4-day endpoint. And it's also useful to
recognize that every trial we've ever done to date
has implicitly included that endpoint. That's
another point that took us a while to get out on
the table. Every trial has included it, because
operationally, if I'm taking care of a patient,
around day 3 or day 4, if you're not better in some
meaningful way, I'm almost certainly taking you off
the study.

But what the FNIH does is give us some
language about how to talk about why I made that decision. So I think that's the strength of the FINH endpoints, is that it codifies, albeit imprecisely -- but it does codify some measures that reflect what happens around that time point, that in the conversation I have with the patient, "Ms. Smith, why do you feel better?" "Well, my cough is better and I'm able to eat." Those are the kinds of things that I would expect to hear, but I might not previously have recorded them on a case report form.

So that's sort of a long speech, and I know it does hurt your head to wrap it around this concept. But that was the heart of it, was to get at a fundamental conundrum in the best way we could.

DR. MOORE: Dr. Weinstein?

DR. WEINSTEIN: So I'd sort of like to follow up the question that Dr. Reller raised about prior antibiotics because I'm not sure what proportion of patients that might be candidates for enrollment in these studies would be excluded
because of prior antibiotics.

Dr. Dubin commented anecdotally that in his practice, it wouldn't be a big deal. But I'd like to ask Dr. File, and Dr. Eisenstein, or Dr. Bartlett to comment on what they think the data would be.

DR. FILE: This is Tom File. And I can tell you, specifically in the FOCUS trials, 42 percent were on a short-acting antibiotic, that if you excluded them would have been not evaluable for that study.

DR. BARTLETT: Well, I think I've already said I think those studies are unrealistic if they're going to have the routine care that's applied in emergency rooms.

DR. MOORE: Thank you. Dr. Sepkowitz?

DR. SEPKOWITZ: Yes. Same issue about previous antibiotics, and Dr. File sort of answered it. But in Dr. File's presentation, you had commented that in the ceftaroline study, X amount had received a short-acting. I assume that short-acting is defined the same way that it was defined
in the other study. Right? The same group of antibiotics, amox clav?

    DR. FILE: Yes. Those would be antibiotics that would be administered more than twice a day in routine schedules, so that would be short-acting.

    DR. SEPKOWITZ: Yes. And you have a comment that one study with one day of clarithro was allowed.

    DR. FILE: In the FOCUS trials, yes. In FOCUS 1, because we tried to enhance enrollment in the United States, where, as John Bartlett said --

    DR. SEPKOWITZ: I understand that.

    DR. FILE: -- that's the guideline, the recommendation. And I think many studies have shown that if you follow the guidelines --

    DR. SEPKOWITZ: I'm not arguing that. So clarithro was allowed for enrollment.

    DR. FILE: One day, correct.

    DR. SEPKOWITZ: Okay.

    Then in Dr. Laessig's presentation on the same issue, you had stated that one dose of one short-acting-only, and then you stratified out the
group that had gotten one, and showed a difference that one dose of one short-acting was associated with a statistically significant difference and outcome. Right? That was your --

DR. LAESSIG: Right. That's all that was permitted. So the two tables showed the priors, which was the dose of short-acting --

DR. SEPKOWITZ: Yes. I'm trying to square the presence or absence of clarithromycin in what Dr. File is saying and what you're describing.

DR. LAESSIG: I can't --

DR. MOORE: Yes. Dr. Valappil?

DR. VALAPPIL: I would like to follow up on Dr. Eisenstein's presentation on the daptomycin studies that, just diverting onto a different area. Based on our analyses of the ITT population, we found that there is a prior effect of the antibiotic therapy, although we are still working on the data analyses and cleaning up the studies.

DR. MOORE: Dr. File?

DR. FILE: Yes. I'm sorry. I just wanted to clarify to Kent here that in the FOCUS 1 trial,
where we had the one day of macrolide, that was not
considered to be a prior antimicrobial agent before
enrollment in trial. I mean, patients enrolled in
FOCUS 1 all received, after enrollment, one day of
clarithromycin. Now, 40-some percent of those,
even before enrollment, had a one dose of a short-
acting antimicrobial agent. Okay?

DR. SEPKOWITZ: That clarifies my question,
yes.

DR. MOORE: Dr. Temple, did you have a
question?

DR. TEMPLE: It was really about the prior
discussion that Ralph had raised. The focus on the
short period, as is common in lots of trials, is
looking at the time when differences between
treatments are greatest. So that's the time when
you want to look. And powering the study for that
purpose seems great, even if the endpoint isn't
perfect, as everyone seems to agree it's not. But
that still makes total sense.

Then looking at the later ones, somewhat
less rigorously if I understand what everybody
accepts, make sure nothing terrible happened that you didn't expect. But you're still focusing on the place where the difference is largest, always a good thing to do.

DR. MOORE: Dr. Neely?

DR. NEELY: I wanted to go back to the primary endpoint that's under discussion for the day 4 and improvement in symptoms. It always makes me a little uncomfortable when there's a subjective criteria for a primary study outcome, and there is obviously a huge, subjective nature to this. Much of the data is probably based on studies that were not placebo controlled, or at least blinded, and so there's a lot of bias potential there.

Has there been discussion -- I didn't see it in the documents that we were given before the meeting -- about who is going to make those assessments, especially in the setting of altered mental status for the patient, who may not be able to say that they have pain or rate their pain? So that's the first question.

Then the second, therefore, has there been
some attempt to, perhaps, objectify those criteria in some way, to rate the pain, to rate the sputum production beyond just mild, moderate, severe?

DR. MOORE: Dr. Cox?

DR. COX: Yes. Thank you. You raise a good point, the issue of measuring the endpoint in a standardized fashion and as consistently as possible as one moves from trial site to trial site.

It seems that this is an area that would benefit from some additional work, as far as the type of instrument or tool that one might use to actually make these assessments. We do encourage, in the 2009 guidance document and other guidance documents, that as phase 2 is being approached, that this might be an opportunity to try and develop those methods for more standardized measurement.

So you raise an important point. I think it's an area that deserves additional development and attention in phase 2 to the extent possible. And the hope is that this is something that we'll
see in the future. In the meantime, we may be faced with a situation where we're dealing with interim endpoints, if you will, as additional work is done, to get to more standardized methods.

So thank you for your question.

DR. MOORE: Before we go on, Dr. Goetz, you had another question. I just want to make sure that we use our speakers' times efficiently.

If there are questions, general questions, about the question at hand, we can discuss those after lunch, but I'm not sure how long we're going to have the speakers who presented earlier present. So if we can, try to address the questions relative to their presentations. Dr. Goetz?

DR. GOETZ: I think my question really referred back to an issue that Dr. Rex raised, so maybe we can pass on that in interest of addressing the issues from our other speakers.

DR. MOORE: Okay. Thanks. Dr. Follmann?

DR. FOLLmann: This gets back to the prior antibiotic use. And Dr. Valappil said something that I thought was kind of interesting. Earlier
today, we saw Dr. Laessig report that prior antibiotics did matter, that they were able to mask an inferior drug. And even before, Dr. Eisenstein had -- and by the way, that analysis is on about 500 people.

Earlier, Dr. Eisenstein looked at the daptomycin trial and concluded that the short-acting antibiotics still revealed an inferior drug, and Dr. Valappil just seemed to contradict that. So I was wondering if you could say a little more about the effect of short-acting drugs in the daptomycin trial.

DR. VALAPPIL: We're still looking at the daptomycin trial. No, I wasn't -- actually, what I was trying to stay is that prior antibiotics have an effect, based on the ITT analysis we have done on the daptomycin studies.

For only short-acting, we found that it's around 78 percent versus 76 percent for the daptomycin. The comparator was ceftriaxone. And for the long-acting, it was around 66 percent to 68 percent. So we still see an effect of prior
antibiotic therapies for the -- affecting the
clinical outcomes.

Sorry for the miscommunication.

DR. MOORE: Dr. Rex?

DR. REX: Thank you. So that question
actually leads to the thing that I'd like to ask
the speakers most broadly. A lot of the discussion
today is going to need to focus on the balance
between what you'd like to do and what you can do.
And please understand that I'd prefer to do a
perfect, clean trial. There's no doubt that you'd
like to hit all the criteria that you've heard this
morning, because it'd probably be a cleaner trial.
But realistically, it's not going to be possible.
You can't make companies work in this area. You
have to make them want to work in this area. And
one of the best ways to make them not want to work
in this area is to make the trials such that they
can only be done in a geological time frame.

So it really does matter that we think about
where we can make trade-offs. Some trade-offs may
be unacceptable; others may be acceptable. And so
I think that's the question I'd be most interested in pointing out to speakers before they disappear, is do you have a thought about -- is it the case that there are no trade-offs that are acceptable? Only perfect is acceptable? Or are there places where you could identify a simple trade-off, that you've heard some of the ideas about how those might impact feasibility?

That's the theme I'm really most interested in.

DR. MOORE: Does anybody have a specific comment to that? Dr. Bartlett?

DR. BARTLETT: Yes. I think it's an easy answer for me, not having done these studies. I think everybody in the room wants a perfect study, and I think nobody in the room says that they're going to be able to do them in the United States, unless you allow a short-acting antibiotic. You just can't do those studies in the United States.

But Tom File is probably a much better person to answer the question because he's done those studies. I mean, how many people in the
United States got entered into FOCUS without a holding antibiotic?

DR. FILE: Yes. It was 3.8, so, I mean, it does illustrate --

DR. BARTLETT: 3.8 percent

DR. FILE: 3.8 percent. Right. It does illustrate the significant impact that that criteria had, I think, on enrollment. And so I think this is a very significant issue that you have to consider, concerning feasibility of these trials.

DR. MOORE: Dr. File, just a quick clarification, if I may. The other large percent of patients who received an antibiotic and were able to be enrolled, my guess is that most of those patients did not receive the antibiotic in the emergency room, but a majority of them probably received the antibiotic from their primary care physician; and it failed, and then they came to the emergency room.

Is that correct or incorrect?

DR. FILE: No. Actually, I would say, most
of those actually received a dose of an antimicrobial agent -- well, it's probably both of those considerations. But a high percentage actually did receive an antibiotic in the emergency room as they were being assessed for enrollment.

DR. MOORE: Thank you. Dr. Bennett?

DR. BENNETT: Tom File, I have a question for you about if there are differences in the quality of symptom data that we're collecting. I could imagine a study nurse going to a hospitalized patient's room, and saying, "How are you doing?" and taking a very detailed study. I could imagine a discharged patient talking to a family member and saying, "How is Uncle Gus doing?"

So what is an acceptable way of collecting the data? Because it might impact on the quality of the data at an earlier time point, where they're more likely to be in the hospital, and a test to cure, where they're more likely to be at home.

DR. FILE: Well, I think this just states that you have to have well-trained nurse practitioners or study coordinators who have
standardized training in how to assess that, and so that all patients in these trials, whatever the site is, are assessed in a very standardized way. And if you have well-trained study personnel, that can be assessed.

I realize that by relying just on the patients to give them information probably is going to be very difficult, from a standardization standpoint. But if you ask the right questions, everybody asks the same questions in the same way, or at least in a similar way, I think you're going to get standardized data.

DR. MOORE: Thank you. Dr. Sepkowitz, and then Dr. Shyr.

DR. SEPKOWITZ: To the people who spoke earlier, we had a wide range of mortality rates. And this group would I think benefit by coming to some sort of consensus about what we're gravitating around.

Administrative Medicare-types of datasets are showing us a 7 to 11 percent mortality. I think the best studies are the prospective studies
that were done with the drugs, and that shows
2 percent-ish, across the board, except for dapto
with 4 percent.

It would help us if you guys could put a
number around it a little bit. Eleven percent is
really high and draws a lot of emotionality, and
probably unjustifiably so. I think my sense is
that it's closer to the 2 percent. But every
speaker gave a different number, and I'm wondering
if you could comment on why you think your number
is better, I guess, because I think mortality is
what we're here about.

DR. FILE: Well, the 11.9 percent mortality
rate that I mentioned is directly from the CMS
Hospital Compare database, which looks at the
Medicare patients. So you're talking about
patients that are older. I mean, we've already
mentioned that age is a significant risk factor, so
you're talking about patients over the age of 65.

Now, I assume that, John, what you
mentioned, the 7 percent, takes all comers, I mean,
which would be --
DR. BARTLETT: Forty-six emergency.

DR. SEPKOWITZ: That was an administrative dataset also.

DR. FILE: That was 46? Okay. That was 46 emergency room. So you're talking about a little bit of a different patient population.

DR. EISENSTEIN: Just one additional comment that may be obvious to the committee, that when one does a prospective phase 3 trial, you're looking at a more homogenous population that excludes the sickest and the least sick. And we know this from our daptomycin bacteremia trial, for example. The mortality rate on both arms was 15 percent. The standard reported rate of mortality in staph aureus bacteremia is 25 to 35 percent. But we were excluding individuals who were moribund on admission to the study. So, presumably, this occurs with pneumonia trials as well.

DR. SEPKOWITZ: Right. But that's as we try to get an understanding of a non-inferiority, this becomes a critical number. And it's not helpful to have a 2 percent to 11 percent for us to play with,
which I know you appreciate.

DR. BARTLETT: Yes.

DR. MOORE: Dr. Shyr?

DR. SHYR: Yes. I would like follow up the 3.8 percent, the pre-antibiotic use. So what percent of the patients, before they arrived at the ER room, got that?

DR. FILE: I can't answer that specifically, at least based on the information I have. Maybe other representatives from that study can. But that 3.8 percent is just the percentage of patients enrolled from the United States. And I'm just saying that a lot of that low percentage is due to some of the restrictions of these criteria, which includes the use of prior antibiotics.

DR. MOORE: Dr. Goetz?

DR. GOETZ: I wanted to re-explore issues regarding differences in infrastructure that allow for rapid enrollment of patients. I wonder if Dr. File might comment on -- and this goes back to one of Dr. Floyd's issues -- that thousands of patients are enrolled in studies of cardiovascular
disease within several hours. And the point was made, why can't this be done in infectious diseases?

But Dr. File has extensive involvement in enrollment of patients in studies of pneumonia. Can you comment on the differences in infrastructure, perhaps, that might facilitate rapid enrollment of patients in cardiovascular studies and, perhaps, the timing of enrollment of patients in studies for community-acquired pneumonia, from the moment they hit the ED to the moment they actually get enrolled in studies?

DR. FILE: I think it's a difference in the structure of how patients are identified in the ER. I mean, I know -- because our hospital has contributed to the ISIS studies and then the TPA studies for strokes. And as soon as any of those patients come in the ER, I mean, those study personnel are right there to evaluate.

Now, what we've done in the past, at least from our setting with the pneumonia trials, is that we have study nurses that will sort of survey the
ER through the computer and see when patients are coming in through pneumonia. But we really rely on the ED docs telling us when there is a patient with pneumonia. They call us, and so we get down there, but we're not down there right at the time when the patients enroll.

I think, in this NIH study that I described, that will start enrolling next year, as I said, we're going to have study nurses in the ER. I said 18 hours. When I think about it, my math wasn't correct. It's actually 16 hours a day, from 10:00 a.m. to 2:00 a.m. the next morning, but seven days a week.

So we're going to have the study nurses right down there. They're going to be well-trained. As soon as somebody comes in that looks like it's pneumonia, they're going to be evaluated. And we're hoping that the consent time will be reduced from an average of two plus hours right now to less than one hour, as we have well-trained study nurses, and gives the same information, and comprehensively evaluates each patient who has
pneumonia right at the time of the ER.

So I think that may explain the difference. I think it's just a difference in the structure of how patients are identified in those trials and their priority given as soon as they reach the ER. We're going to now give pneumonia the same type of priority as some of those other trials.

DR. GOETZ: I'm interested in sort of the generalizability of that. And my understanding is that there are incentives for every facility to have a rapid response to people who may be having a myocardial infarction; in other words, that there are hospitals across the country that deal with people with heart attacks, have these structures in place with a very rapid response as time to cath, which is a critical outcome measure. And, thus, that has facilitated enrollment of patients into the study.

Do you think that that -- and so I'm concerned on two points, the generalizability of the infrastructure that you have with your NIAID support, other facilities in the United States, and
also the impact on other structures that make replication of those very rapid times for getting people on studies for cardiovascular disease, relevant to infectious diseases.

DR. FILE: It's very interesting because, as John mentioned and I mentioned, we talked about the CMS core measures that eventually was eight hours, then it went to four hours, and now, it's six hours. And the real concern was, when we went to four hours, there was a lot of comments that we may be jeopardizing patients, for example, who come in with acute myocardial infarctions or good strokes, and we'll be paying attention to the pneumonias rather than those patients.

But I think the CMS rebut was, well, we figure that, based on the large database studies, that we are going to save thousands of lives by using this 4-hour core measure, as they are saved with the acute response to a myocardial infarction or strokes.

Your question is a very good one. What is the feasibility of having somebody in the ER, every
ER in the country, to evaluate everybody who comes in with pneumonia? And we don't know that. I mean, we don't even know if the study we're going to do is going to show improvement, but we have to see if we can do that.

Actually, the study is primarily designed to show -- it's an interventional trial to show that by using pathogen directed or point-of-care diagnostic tests to identify a pathogen, we can actually improve care, reduce resistance, reduce adverse events, and all this.

So it's really more of an interventional trial to look at the outcomes of how we approach patients. Rather than always giving empiric therapy, we're going to try to give focused therapies. So until we do that trial, I think we're going to have difficulty I guess convincing people that they have to approach pneumonia in the same manner as they approach acute MI or acute stroke.

DR. MOORE: Dr. Fleming? We're over time, so we won't be able to take a whole lot more
questions, but we have time for just a few. So
Dr. Fleming?

DR. FLEMING: A clarifying question for
Dr. File. I very much appreciate the insights he's
provided about the likely influence of prior
antibiotic treatment. And you've shown us, again,
the daptomycin data, and you've shown us the
ceftaroline data, wherein the daptomycin data, as
now many people have recognized, giving a prior
antibiotic, there was no difference. If you
didn't, there was -- you were able to see the
inferiority of daptomycin. And in the ceftaroline,
when you didn't have prior antibiotic, you could
see the superiority of ceftaroline that was masked
when you had received prior antibiotics.

Now, if I understood your comment when you
were asked how hard is it going to be to get people
without prior antibiotics, and you were referring,
I think, to a 3.8 percent or something like that;
yet the analysis that you're showing in the
daptomycin trial, by my data here, we only had to
exclude 189 people under the categorization of
prior effective anti-bacterial treatment. The
group that was sensitive, the ones that we were
calling no, was 551 people.

So we weren't excluding 96 percent of the
data in order to have the sensitivity; we were
excluding only 25 percent of the data to have the
sensitivity. And in the ceftaroline data, I don't
have the exact numbers, but the width of your
confidence interval for that didn't-receive isn't
very much larger than those that did. So it would
suggest to me that a substantial fraction in the
ceftaroline trial also were characterized as people
that hadn't had prior effective anti-bacterial
therapy.

So I'm getting a very different sense from
the data that if we're rigorous about this, so we
don't give prior antibiotics in a way that dilutes
the sensitivity to an inferior therapy, it doesn't
sound like we have to exclude 96 percent; it sounds
like we have to exclude 25 to 50 percent of the
people, according to the actual data that we're
showing here.
What am I missing?

DR. FILE: Well, What you're missing is, we said that it would be good to have studies done in the United States in order to oblige the idiosyncrasies of microbiology and practice standards. And those studies that you're quoting were almost entirely done in other countries. So if you're going to do them in the United States, you can't do that. If you're going to do them outside the United States, you might be able to do it.

It makes me a little uncomfortable to say you're going to be enrolled in a study, and you're going to have a delayed enrollment -- you're going to have delayed antibiotics because you participate in the study, if that is, in fact, the consequence of participating in a study.

DR. FLEMING: So my understanding is that this is very feasible if we don't restrict to the U.S. -- we're not needing to, in fact, exclude large fractions of people -- and that we haven't rigorously tried, in the U.S., to validate that we
can't do it. It sounds like we haven't successfully done it, but we can't say we've rigorously tried and been unsuccessful.

DR. FILE: Well, I mean, we tried, but the protocols allowed us. And so with the core measures, as they are now, and with the paradigm of the ER physicians wanting to make sure that they comply with the core measures, which are actually pay-for-performance measures, the point is that they are going to give an antibiotic -- as the one presenter from the ER mentioned earlier, they're going to give the antibiotic within 4 to 6 hours to make sure that they comply with that regimen.

I'm not sure I'm responding correctly, Dr. Fleming, to your question, but all I'm saying is that that -- I'm just pointing out that in the FOCUS trial, the FOCUS 1, which included patients from the United States, of the 600 and some patients, only 3.8 percent were enrolled from the United States.

Now, why is that? Well, I'm just saying that there were many barriers. And I think the two
barriers that -- or the primary barrier was, quite honestly, the length of time it takes for the ER docs to call us to get consent, and they wanted to make sure that they were within the 4- to 6-hour period. And if they thought -- and they’re a very busy ER, and by the time they see the patient, it may already be three hours because it's when they sign into the ER, not when they see the patient.

Now, I realize that many of the ERs now have triage systems so that if a patient comes in with a fever and a cough, they are going to be seen earlier. But we know that 90 percent of the patients coming in with fever and cough don’t have pneumonia. I mean, they may have bronchitis. They may have viral infections or whatever.

So I'm a little concerned by the response by the physician saying that they would get a chest x-ray, then give an antibiotic, and then go on their way. Well, they've already received an antibiotic before you even know they have pneumonia. And so that's the concern.

This may not be what you asked, Tom, but
anyway, that's my response.

DR. FLEMING: It wasn't what I asked. My comment was, the data that we have suggests that it's very feasible to be able to enroll cohorts that have not had prior effective antibiotics, but your point was, but not in the U.S. And my comment was -- my question was, have we tried? Have we done a trial in the U.S. where we specifically indicated that you shouldn't have prior antibiotics, and we were unsuccessful? Have we tried?

DR. MOORE: Dr. Laessig?

DR. LAESSIG: I'd sort of like to try to respond to that. I mean, I think the question is, of sponsors trying to enroll patients in CAP studies in the U.S., of the subjects -- or the potential candidates they screen, how many are excluded on the basis of receipt of prior effective antimicrobials?

So I don't know if there is any sponsor here who's willing to get up and share that kind of information. We don't actually get that sort of...
information, except for anecdotally.

DR. MOORE: Dr. File, did you want to respond to that?

DR. FILE: I just wanted to say, again, to Dr. Fleming, I mean, actually, our NIAID study is designed so that these patients, as they come in the ER, will not receive any short-acting antibiotics. So we're hoping to be able to do that. But so far, we just have to see how successful we are.

DR. MOORE: Dr. Reller?

DR. RELLER: Though one might debate the extent of the effect, it seems to me there's general agreement there is an effect of prior antimicrobials. So I'd like to tie up what has just been said with the feasibility question and balance.

We've heard on the one end that in the United States at least, no way, no how, not feasible, not going to happen, excludes participation. On the other hand, Dr. Burns [sic] said most patients are not getting antibiotics when
they come, but clearly articulated, very forthrightly I thought, that the primary driver of early antibiotics are the financial incentives. He didn't say, but one can imagine a great deal of administrative incentives in addition to pay-for-performance.

So this is the question. What effect could, should, might the changes that he articulated coming down in January 2012 have to eliminate the administrative fiscal -- he didn't say this, but presumably that would be the case, where that was not part of the reimbursement mechanism, that would change the whole landscape -- not getting into how long it takes people to change habits, but, theoretically, there would be no regulatory constraint on enrolling patients with no prior antibiotic therapy, which, it seems to me, there's general agreement would be the ideal thing, and is it possible that this change would make it feasible?

DR. MOORE: Good point. I think that it's impossible to predict, but you're right. It will
change the landscape considerably.

Dr. Temple?

DR. TEMPLE: Just one point. It sounds like getting consent is at least a part of the difficulty here. And it's worth exploring what has been done in the cardiovascular area. In that case, they knew that delay of giving streptokinase or something like that was lethal, so they'd be killing patients, and they used very abbreviated consent forms.

This is actually described in a publication for the Gissi study, and it's probably not talked about as much as people would like to, because people are uncomfortable with abbreviated informed consent. But it's probably worth talking to the people who do those about how they've done it, and maybe already have. But they get consent in minutes, and it's clearly different from the full 20-page consent form that's typical of most studies. So there may be some room for improvement there.

DR. MOORE: Thank you.
Dr. Reller, this will be the last one.

DR. RELLER: I just wondered, when I heard the point -- I'm fully aware. And the IDSA in the position papers address the question of HIPAA and its appropriateness or inappropriateness as part of the whole consent apparatus.

But one really has to wonder, just from a common-sense standpoint, whether a 20-page consent form -- I'm not saying that IRBs don't require it -- whether there is any possible way that a sick patients is truly informed when having to weed through 20 pages. I think that's wishful thinking in the extreme, and maybe something should be done about that, along with, if there were enough players, so to speak, that said, wait a minute, this is ridiculous.

DR. TEMPLE: I don't think anybody disagrees with you. It's just very hard to stop because people are afraid to.

DR. RELLER: Maybe that makes it all the more important to try.

DR. TEMPLE: But you're right. Many people
say these get in the way of informed consent, and how could they not? So you're right.

DR. MOORE: Thank you. Thank you very much for that discussion.

All right. It's 12:25. We're 25 minutes over from our break time, so let's do this. We'll break for lunch. We'll reconvene again an hour from now. Let's make it 1:30. I recognize we'll be starting a little late, but we've had quite a bit of discussion already.

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 12:25 p.m., a luncheon recess was taken.)
AFTERNOON SESSION

(1:32 p.m.)

Open Public Hearing

DR. MOORE: So we’ll proceed now with the open public hearing. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency of 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, this 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, the 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 and 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, treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chair.

Thank you in advance for your cooperation.

Our first speaker is going to be Dr. Gary Noel, the vice president and chief medical officer of Paratek Pharmaceuticals. Dr. Noel?
DR. NOEL: Thank you. Good afternoon.

As you've said, my name is Gary Noel. I'm the vice president and chief medical officer of Paratek Pharmaceuticals. I am also a member of the FNIH group that has made recommendations around the clinical trial design for community-acquired pneumonia.

Paratek Pharmaceuticals is a privately-owned, privately-held biopharmaceutical company which is engaged in the discovery of new therapeutics for the treatment of life-threatening infectious diseases and other serious infectious diseases. It has as its mission to address the major worldwide problem of bacterial drug resistance through the application of proprietary technologies related to tetracycline-derived chemistry.

The purpose of my making comments to the committee this afternoon is to underscore the importance of two factors that I hope you do consider in advising the Food and Drug Administration, and that is urgency and
decisiveness around community-acquired bacterial pneumonia guidances.

Finalizing a process, which is now coming upon its fourth year, will have great and a very positive impact on the development of molecules that will hold the promise of meeting some of the important, evolving unmet medical needs in community-acquired pneumonia patients.

Paratek's lead compound, omadacycline, or PTK796, is an aminomethylcycline that has demonstrated a broad spectrum of activity against clinically important Gram-positive and Gram-negative pathogens. This has been accomplished by chemical modifications which make PTK0796 not susceptible to the two major mechanisms of tetracycline resistance, active efflux and ribosomal protection.

PTK0796 has shown activity in vitro and in animal models against two of the so-called escaped pathogens, namely, drug-resistant enterococcus and staph aureus. In addition, PTK0796 has activity against many of the Gram-negative bacteria that are
considered to be escaped pathogens and that are 
resistant to the two most widely used classes of 
antibiotics, namely betalactams and 
fluoroquinolones.

The molecule has excellent activity against 
pneumococcus, including tetracycline-resistant 
isolates of pneumococci and has activity against 
all the leading atypical bacterial causes of 
community- as well as hospital-acquired pneumonia.

PTK0796 has advanced through pre-clinical 
phase 1 and phase 2 clinical studies, and that work 
has supported the drug's development in two major 
indications, acute bacterial skin infections and 
community-acquired bacterial pneumonia.

Developments of the drug in skin infections 
is the most advanced, and it's the most advanced 
largely because it's been able to meet the 
requirements that the FDA has set out regarding new 
trial designs for acute bacterial skin infections.

However, the developments of PTK for therapy of 
community-acquired pneumonia has not moved along as 
quickly. The process of preparing for a phase 3
program in CAP has been affected considerably by
the uncertainty that has accompanied decisions to
change registrational or primary endpoints, primary
endpoint populations, and inclusion/exclusion
criteria.

In addition to this uncertainty, there has
been great concern that many of the proposed
changes for these phase 3 programs would make
trials unfeasible, and we've heard a lot about that
this morning, especially if the program were to be
conducted in the United States.

I believe Paratek Pharmaceuticals is part of
a larger community of drug developers who strongly
support the FDA's prompt resolution of community-
acquired bacterial pneumonia guidance. This needs
to be done immediately if promising new agents such
as PTK0796 can move into those indications.

It's entirely appropriate for physicians,
patients, and societies to be concerned about the
paucity of new molecules aimed at addressing anti-
bacterial resistance. The pipeline is clearly dry.
However, let's be certain that the powerful message
does not completely overshadow a more pressing concern. And that concern at today's meetings could have great importance in addressing it. Specifically, we have few agents that are currently promising as new therapies for community-acquired pneumonia. We need clear, feasible, and medically sound pathways for the development of these agents.

In closing, I want to recognize the hard work that has taken place to get us this far. We've heard various stakeholders over the course of today's meeting, as well as previous advisory committee meetings, comment on an assortment of draft guidances. However, publication immediately of a medically sound and feasible guidance that provides a clear path for drug developers is greatly needed, and we appreciate the committee's help in bringing this closure to the FDA with this advice. Thank you.

DR. MOORE: Thank you, Dr. Noel.

Our next speaker will be Dr. David Friedland, vice president of clinical sciences at Cerexa.
DR. FRIEDLAND: Good afternoon. I'm David Friedland, vice president of clinical sciences at Cerexa. Cerexa is a wholly-owned subsidiary of Forest Laboratories, and I'm a full-time employee. So I'm going to cover two quick topics in my presentation, first of all, support for the ITT or modified intent-to-treat population for the primary analysis.

So we've taken the clinical cure rate of test of cure, broken down by identification of pathogens at baseline. So in the top row, you have the population with at least one typical pathogen identified, and you see on the very right-hand side a 7.6 percent treatment difference in favor of ceftaroline. The second row is the population with no pathogens. And I'd just like to point out, first of all, that only about 30 percent of patients, 26 we saw this morning, have a typical bacterial pathogen. The population with no bacterial pathogen -- there was a 6.1 percent treatment in favor of ceftaroline. And with the atypical-only population, there was no treatment
difference, and this is what you would expect, as neither drug has activity against these pathogens.

So now looking at the day-4 results, you see a very similar picture, although the no-pathogen population doesn't have quite the same treatment differences we saw in test of cure, but still, it showed that the majority of those patients should have had a bacterial pathogen that just wasn't identified, so showing the same etiology.

So these two slides, I think, support the use of the overall population in your analysis. By excluding people with no pathogens, I think you're losing a lot of vital information.

The second topic I want to cover is the use of prior antimicrobials. We've heard a lot about this today. And you saw a presentation by Dr. File and you saw a presentation by Dr. Laessig, showing that in the ceftaroline studies, that there was an effect of prior antimicrobials, and there was a short-acting one dose of prior antimicrobials.

However, I want to point out that, even with these prior antibiotics, it was still possible to
detect a treatment difference using the overall population. So this is a busy slide, but it's basically the same slide that Dr. File showed this morning. And I want to just draw your attention to the right-hand side. That's the treatment difference, the bars, of ceftaroline minus ceftriaxone, with a 95 percent confidence interval around the treatment difference.

What this slide basically shows, that even with prior antimicrobial therapy included, ceftriaxone would not have met non-inferiority against ceftaroline. And that's showing by the upper bound of the 95 percent confidence interval being greater than the positive 10 line that I'm showing you there.

The same conclusion can be made from the daptomycin studies, as we saw this morning. So even with prior antimicrobial therapy, it was still possible to see a treatment effect. I also want to point out that FDA doesn't just look at the primary endpoint. If that was the case, that'd be great; we'd only have to write a 10-page efficacy
document. However, we do hundreds of analyses. And when you do it by subgroup and those data don't support your primary analysis, it'll bring into question your primary analysis. So it's not black and white, just one analysis and you're done.

It's also important to note that in the ceftaroline studies, limiting prior antibiotics to only this one dose of a short-acting antibiotic and not allowing a full course of macrolide therapy, as we heard this morning, only 2 percent of the total population of the CAP studies were enrolled in the United States. It was 3.8 percent in one study and zero in the other study.

With this regard, we approached 198 centers in the United States and only 13 agreed to participate in the study. And when we did our feasibility and said to them all, "We don't allow any prior antimicrobial therapy as well," zero said they would participate. So if we disallow all prior antibiotics, we'll pretty much just eliminate the United States from future CAP studies.

So then there's another potential issue with
prior antimicrobial therapy, and that's if you give prior antimicrobial therapy, does it affect your recovery rate or baseline pathogens?

So here, we looked at the whole population, did it affect isolation of pathogens. And we only looked at typical pathogens. And there was about a 5.5 percent decrease in recovery if you received prior antibiotics. So that could be a problem.

However, when we look by pathogen, you can see it has no effect on the Gram positives. It did not affect streptococcus pneumoniae. It didn't affect staph aureus. It really affected the Gram negatives, and it affected the parainfluenzae and the other less common Gram negatives more commonly than anything else. And when FDA does their pathogen assessments, those organisms, where there is an effect, weren't classified as true CAP pathogens.

So if you look at our label, the ceftaroline label, you'll see that none of those organisms that are in our label were affected by the prior antibiotic therapy. Thank you.
DR. MOORE: Thank you, Dr. Friedland.

Our next speaker is Dr. Shlaes with Anti-Infectives Consulting.

DR. SHLAES: Hi. My name is David Shlaes. I'm a consultant for the pharmaceutical industry. And I want to talk to you today about the trial design requirements for CAP. In terms of disclosures, I'm employed by a number -- or I'm consulted by a number of companies, and it's a long list, so I've referred you to my website for the list.

I am an IDSA member, and I did participate in drafting the Bad Bugs, No Drugs white paper. The opinions that I'm expressing are my own. I've been around for a long time. I started in academia, where I spent 16 years working on antimicrobial resistance. I then went on to a 15-year career in industry. So I've been working on antimicrobial resistance and antimicrobial product development for about 30 years or so, which is hard to believe.

I strongly believe that we need a strong,
vibrant, scientifically based and interventionist FDA to ensure that we have efficacious and safe drugs. To help combat infections caused by resistant pathogens, we need a robust pipeline of new antibiotics. In recent years, unfortunately, I think these two concepts have been mutually exclusive. And I'm hoping, with the FDA's current focus on trial feasibility, we'll start to get this paradox into some balance.

So I think the FDA is to be commended for their approach to making trial design for community-acquired pneumonia feasible, at least as far as the required trial size is concerned. An NI margin of 15 percent within the microbiologically documented patient population and allowing pooling across two studies or allowing the conduct of a single study makes these trial sizes feasible. Going back to a 10 percent margin for the microbiologically documented group would take us back to infeasible numbers. As you've heard, the proscription against prior antibiotics remains a considerable problem for trial feasibility still.
So I want to tell you about one of my clients who recently ran a phase 2 trial for an oral antibiotic. The trial sites were in the United States, Canada, Hungary, and Poland. First of all, as you just heard from Dr. Friedland, they also had difficulty recruiting U.S. investigators because most sites didn't want to participate because of the restrictions on prior antibiotic use.

Of interest, in both U.S. and ex-U.S. sites, among patients who had prior antibiotics -- and I'll get to those numbers in a second -- there was a high percentage of use of long-acting antibiotics, which was problematic.

So in this trial, this company screened 860 patients, and they were able to enroll 32; 220 of the 860 that were screened were disqualified because of prior antibiotic use. They did try and address the issue of ER process but were unsuccessful in doing so, in spite of considerable effort. So they ended up with, so far anyway, 32 patients out of 860 screened. They're still trying
to run the trial, mostly outside the U.S. in other areas.

There is the issue of endpoints that you've heard about, and I'll just point out that there are many physicians who believe that these early endpoints are less relevant than the traditional test of cure, as Dr. Eisenstein mentioned. And my belief is they should be secondary, not primary.

In this regard, I'm surprised that the FDA does not want to use the newer methods for establishing treatment effects, specifically M1, such as pharmacometrics. Why can't we use pharmacometrics to establish M1 and then derive our M2 based on that? Europe is certainly open to thinking about that.

This was a slide that was presented by me, actually, representing pharma at the time, to the FDA back in 2002. And what it talks about is trying to strike the right balance, and that's the word we've heard several times today, because what we need is we need new antibiotics. For companies who make antibiotics, which is mostly the
pharmaceutical industry, we have to have a balance between cost of development and having barriers to entry that we can overcome. Right now, at least in CAP, that's not the case. We are definitely out of balance.

So the number of ongoing phase 3 trials for new antibiotics for community-acquired pneumonia today is zero. Just because resistance is not an issue for CAP, or for that matter, other respiratory tract infections today, does not mean it will not be a problem in 10 years. And the example I put forth is vancomycin-resistant enterococcus. Who would have ever thought that that would occur, especially the way that it occurred?

So, in conclusion, I think in the briefing materials for the meeting, the FDA has made very clear progress, but we're still not there. We need to change our approach to enrolling patients who have had prior antibiotics. I suggest a stratification approach.

We need to keep the NI margin reasonable for
oral antibiotics if we ever want any to be
developed for pneumonia in the future, because if
we can't do that, you won't have any. And my
suggestion there is to use the same criteria that
we use for the IV that you've already proposed.

I think endpoints should be reconsidered
using pharmacometrics to define M1 and, therefore,
M2, for clinical outcome at test of cure. Thank
you.

DR. MOORE: Thank you, Dr. Shlaes.

Our next speaker is Dr. Echols, principal
member of Infectious Disease Drug Development
Consulting.

DR. ECHOLS: Thank you. I appreciate the
opportunity to speak at this meeting. My name is
Roger Echols. I'm an independent consultant, but
an infectious disease-trained physician who's been
in drug development for more than 30 years,
starting as an academic investigator for 10 years
in an upstate medical center, and then the last 25
to 30 years, within industry, developing a number
of drugs.
My comments today are going to be focused just on oral therapy for CAP, which used to be a very common pathway for drug development, but is pretty much a neglected stepchild at this point in time, although I do point out and commend the division for adding this as the last question in the last section of their discussion, where they've asked for any advice on performing clinical trials of oral anti-bacterial drugs.

Then they say in parenthesis, "When an intravenous formulation is not available," and I would contend that it's not necessarily because an intravenous formulation is not available, but in fact, an intravenous formulation may not be appropriate for that patient. One must put into context that 70 percent of community-acquired pneumonia in the United States is treated entirely as an outpatient with oral therapy.

The difficulty in coming up with clinical trial design criteria really goes back even before the first workshop, when I was working at Replidyne and we had an oral penem called Faropenem, which
was not approved at its initial NDA, but we spent
much of the year 2007 trying to come up with an
acceptable study design, an agreement with the
agency through a special protocol assessment. But,
ultimately, the division was unable to give us any
final advice, and they alluded to -- and in fact,
they've had several workshops and AIDAC meetings on
this very subject, trying to resolve some of the
apparently unresolvable issues.

In the 2009 December meeting, the sort-of
last question of the day focused on oral therapy
for CAP. And the conclusion of the committee was
that they would like superiority trials.

Around the same time, the product
azithromycin, which was being developed by Advanced
Life Sciences, had its NDA turned down, and they
also went through a special protocol assessment in
2009 and into 2010. And they actually announced
with some enthusiasm the fact that they had reached
agreement with the agency for a superiority design
study for an oral drug for CAP.

However, when one looks at this study, it's
really not feasible. It was an 800-patient study, all of whom would have had to have had a positive antigen screen for streptococcus pneumoniae and presumably all of whom had strepto pneumoniae as their etiology. Their hypothesis testing for superiority was reasonable, but the point is that when one considers the number of patients you would have to screen -- and I mean more than just screening. You would have to enroll those patients to at least do the antigen-specific test.

It really comes to the tune of about 10,000 to 14,000 patients to get the 800 patients that have a positive urinary antigen. That clearly was not feasible. Advanced Life Sciences ceased operation in 2011 of this year, or May of this year, and the asset, azithromycin, is now owned by a small bank.

To this observer, there is really no feasible regulatory pathway for approving an oral drug for CAP. The only way is to have both an IV and oral formulation, and you do an IV/oral step-down and get approval of both formulations. But
this is really not addressing the ambulatory
treatment of community-acquired pneumonia, which is
the vast majority of the patients.

In the current set of guidelines for oral
therapy, the emphasis has been on PORT scores or
PSI scores for the appropriate patients to be
enrolled. And what I'd like to stress -- and this
really comes from a dataset of over 2,000 patients
from the garenoxacin program, which had six CAP
studies. And we analyzed these 2,200 patients by
PORT score for what the etiology of their bacterial
pneumonia was. In fact, there was very little
difference with the exception of mycoplasma
pneumoniae, which was more frequent in PORT I, but
there was no difference, really, in the incidence
of streptococcus pneumoniae across the four or five
different PORT scores.

So, in conclusion, I really think I'm
imploring the committee to really take up the
question of oral CAP. It is an important pathway
for regulatory approval for drugs that do not have
an IV formulation. It's a key indication for any
drug that has a potential for respiratory tract infections.

The early response data, as we've seen and as I've published in the CID proceedings of the first workshop in 2008, there is plenty of evidence for early response differentiation to justify a non-inferiority margin. And I think, certainly, by allowing the pooling of the microbiologically documented ITT population across studies is a very important shift in the division's perspective.

I really do, I want to say, appreciate what the efforts of the FDA have had to bring yet another meeting to discuss CAP, because of the difficulties that we've all heard about today.

Thank you.

DR. MOORE: Thank you, Dr. Echols.

The open public hearing portion of this meeting is 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. And
Questions to the AIDAC and AIDAC Discussion

DR. COX: Thanks, Dr. Moore.

Just to start out, I just want to thank everybody for all the presentations over the course of the day. They've helped to provide some very useful information as we consider the questions. And I did go through the questions during my presentation, but I'll walk through them again now. I'm guessing, after the presentations, the questions are probably even more meaningful than they were this morning.

Critical here is we've made these all discussion questions, so very important to us is to understand the rationale in the thinking. So we really do very much appreciate your describing your rationale as we work through the questions. We find that to be very, very helpful to us.

The first question is, please discuss the merits and limitations of an endpoint based upon improvement in at least two of the four symptoms of cough, amount of sputum production, chest pain and
difficulty breathing, and a worsening of new
symptoms at day 3 to 5 as a primary endpoint for
community-acquired bacterial pneumonia trials.

In your discussion, please comment on a non-
inferiority margin of 10 percent for each of the
ITT or intent-to-treat analyses and possibly a 10,
12.5, or 15 percent non-inferiority margin for the
pooled microbiological intent to treat, or we often
times refer to it as the micro-ITT population, and
this endpoint being based on the historical data
showing a treatment effect on clinical responses,
noted at day 3 to day 5 of therapy.

So we're interested in the endpoint. And
you'll notice in the first question, we're talking
about a symptom-based endpoint. We're also
interested in the non-inferiority margin as it
relates to the ITT and the micro-ITT analysis
populations.

The next question, question 2, so question 2
refers to the options one through three that
Dr. Laessig presented, and they're also in the
briefing document, describing different
prototypical pathways for developing a drug for community-acquired pneumonia. So those are the options we're referring to in this question.

You'll also notice that option 1 and option 2 are quite similar, but option 2 adds signs, things such as fever. So I'm just pointing that out to distinguish what the difference is between the first question and the second question.

The second question, please discuss the merits and limitations of each of the proposed development pathways. That's referring to the options 1 through 3 and trial designs. In your discussion, please comment on the use of improvement or stabilization of clinical signs of pneumonia as a co-primary endpoint versus its use as a secondary endpoint. In option 1, it's a co-primary -- I'm sorry, it's a secondary endpoint -- and then option 2 is a secondary -- I'm mixing it up. Let me start that over. Sorry about that. She reversed the numbers.

So in option 1, it's a secondary endpoint to look at signs, and option 2, it's a co-primary to
have the signs along with symptoms. Sorry about that.

Then question 3, some additional issues, and these are issues that we've talked about over the course of the day. But we're interested in your advice, thoughts, and impressions with regards to a couple of additional issues, the first being one that's been a topic of considerable discussion, the issue of receipt of prior anti-bacterial therapy, how should that be handled in a clinical trial for community-acquired pneumonia?

We've heard the discussion of various different approaches, whether it be exclusion, inclusion, stratification, various limits and such, so it would be very helpful to hear the committee's discussion on that issue.

The next item, number 3, any advice you can provide with regards to methods to enrich the micro-ITT population, so those patients for which we can establish a microbiologic diagnosis in the clinical trial of a drug seeking an indication for CAP; advice on the next issue of mechanisms to
overcome barriers to trial conduct. We've heard
discussion about the emergency room being a
potential area to enroll patients, issues such as
consent, the time that's involved, possible ways to
address that. And then the fourth issue moves
onto a related and important topic, that on
performing clinical trials for oral anti-bacterial
drugs for CAP. We included the proviso, when an
intravenous formulation is not available,
specifically thinking that if an IV formulation is
available, there may be a way to make a
pharmacokinetic link.

So this is, in essence, to try and get a
little bit more at the issue of, if you don't have
that as an option, ways that you might study an
oral formulation, when that, in fact, is the only
formulation you have available for a new anti-
bacterial drug for the treatment of CAP that is in
oral form.

So those are the questions, and I'll turn it
back to you, Dr. Moore.

DR. MOORE: Thanks, Ed.
So I want to have a free-ranging discussion before we start going around the table and taking everybody's opinion. Dr. D'Agostino?

DR. D'AGOSTINO: What did you say you wanted? I was going to comment on one.

DR. MOORE: I was just saying, in general, I want everybody to sort of let it rip, so have your say.

DR. D'AGOSTINO: Okay. I'll let it rip. I find, as we move to one, for example, that it is an uneasiness that it's subjective, but you've lived through this, a number of discussions, and so forth. But I think that it's good to raise that question.

There's also the intent-to-treat analysis, which I'm very much in favor of, but it keeps getting thrown into the discussion, the per-protocol, or the evaluable patients, and so forth. And I think, again, that I would like to see some discussion again, even though guidelines are saying the intent to treat.

But these margins, there's -- and I think
Tom was going through some of the discussion this morning -- there is a database that we can look at and so forth. So I'm quite comfortable with the margins that are there, but they're not the sort of traditional margins that you deal with, that you run into in a lot of placebo-controlled trials, and you come up with an M1 and M2.

So, I mean, I am comfortable with what's being suggested, and we can talk about design 1, 2, or 3, and so forth. But as far as this one, I have comfort with it, and I think they modify the micro-ITT. And I want to congratulate whoever did it. When the early documents were saying mITT for micro, everybody was reading it as modified and so forth.

But I have comfort with this, but I think the issues I've just raised are the sort of throw-around-the-table that we should say something about.

DR. MOORE:  Very good.

Yes, Dr. Sepkowitz.

DR. SEPKOWITZ:  A slightly different issue
that's related to question 1, which is, it's a complicating factor, and I guess if we hadn't waited for you to get this far, we would have not had this. But we need to consider what the impact of rapid viral diagnostics is going to be on our interpretation of data in two ways.

One is all the rhinovirus, and adenovirus, and et cetera, that we're going to find out people have, both as the monocause and if we're going to include or exclude those people and consider that causative.

But I think, more importantly, vis-a-vis this, as someone who's a recent URI sufferer and victim, if someone has pneumococcus and has RSV, and these symptoms don't get better because the RSV is also present, and this is going to be a large proportion, the more sensitive our viral test, how are we going to square that?

So as messy as all of this has been up to now, it's about to get even messier, and I think we have to actually think about how we're going to lay out, going forward, viral single-diagnosis and
viral with bacterial combo-diagnosis, because it's
going to happen. It's going to happen a lot. And
if we're going to have a symptom-based endpoint,
we're going to have to know how to adjudicate it.

DR. MOORE: Yes. Your point is well taken.
And I would just interject that -- Dr. Bartlett
alluded to this. I think that, just my own
personal opinion, we shouldn't insist on molecular
techniques as a provision to conducting these
trials for exactly this reason. There's a lot of
information that's going to be coming out, just
like the c.diff PCR. It's very sensitive, and I
think clinically there's still a lot of debate
about how relevant it is when you have the patients
enrolled in studies, for which I'm skirting the
issue. I won't get into it. It's too difficult.

But Dr. Goetz, you had a point?

DR. GOETZ: My point is different from
Dr. Sepkowitz's, but I'd like to explore the vital
signs component of the response that is a secondary
outcome in the -- let's see if I can say this
right, now -- first non-inferiority design and a
co-primary endpoint in the second non-inferiority study.

I guess, in part, I'm trying to weigh the importance of including that. There was reference made -- one of the critical linkages that we're using in the non-inferiority characteristics is I think the Bullowa studies and others that were referred to, where the response was on the Y axis, if you will. And then the components that went into that response, as I recollect from previous meetings this committee, had a lot to do with a person's vital signs, blood pressure, and such.

Then just sort of amplifying one of the reasons I'm inquiring of this is that in some of the documents that were provided to the committee, there was a comment that these weren't clearly on the causal pathway of disease. But I would maintain, as an editorial comment, that cough is not the cause of pneumonia, which is one of the points that's made, and sputum production is not the cause of pneumonia, but a consequence, just as are changes in vital signs. And my personal
perspective is that people die of pneumonia because they become hypotensive and develop respiratory distress, which is well captured by vital signs measurement.

So anyway, I'd like to go back to what the measures were in the Bullowa study so that we make sure that we anchor our outcomes.

DR. MOORE: Thank you.

Dr. Calhoun?

DR. CALHOUN: Yes. Ironically, a point just to amplify on what Matt said, we heard this morning a number of times that fever was a biomarker, which I think it was characterized at least once as being invalid or unvalidated. In fact, it is part of how we function in the Institute of Medicine terms, feeling, functioning, and surviving.

About the last of our bodily functions that goes away when we're about to die is our ability to homeostatically regulate our body temperature. It's fundamentally important to all biological processes. And I'm, for one, pretty disturbed to hear that fever is just an unvalidated, and perhaps
even invalid, biomarker. I don't view it that way at all.

Secondly, I think biomarker is in the eye of the beholder. As a pulmonary guy, I think that how the lungs function is actually importantly measured -- again, just to amplify something Dr. Goetz said. It's importantly measured by how well we oxygenate blood. And so a metric of oxygenation is not, in my view, a biomarker; it's a measurement of a consequence of the disease. When you move to something like heart rate, or you move to something like respiratory rate, the direct link might get a little less, but, again, they're consequences of disease.

So I'm pretty uncomfortable throwing all the signs of disease away and calling them unvalidated biomarkers.

DR. MOORE: Thank you. Dr. Temple?

DR. TEMPLE: I guess I have a fundamental question I hope people will address, which is whether ITT is the right measurement here. In our guidance on non-inferiority studies, we advocate an
as-treated or some modified thing because ITT, as a
general matter, gives you a bias towards the null,
an inability to find a difference. So although we
say, well, we want to look at both, we generally
like an as-treated analysis as the primary analysis
because it's more likely to be able to show a
difference.

So, for example, if people got another
therapy early, that's clearly going to obliterate
any differences between the two drugs. And I think
there needs to be some discussion of whether you
really want to count them in your primary analysis.

A lot of the discussion has been whether you
count only people who have a bacterial designation.
That's a different question. I'm not questioning
that. That seems like a good analysis for the
pooled analysis. But the assumption seems to be
that the best analysis is counting everybody, no
matter what happened to them. And that is not
usually the position taken on non-inferiority
studies because it obscures differences.

So I'm sure Ralph and Tom will have views.
DR. MOORE: Dr. Rex?

DR. REX: There are a couple of us at the table who were part of the FNIH group, and I thought I might make a comment or two about the comments that Bill Calhoun just made. And so I guess the other person -- Tom was in the group.

Who else -- is there anybody -- I guess it's just -- oh, Dean. Sorry. Duh. Sorry about that, Dean. Thank you.

So my comment, my response to you is going to be carefully worded. First, I want to say I actually agree with your cognitive dissonance. It drives me a little bit crazy to think about an endpoint that doesn't involve what I think of as critical measures of how somebody functions. So your comment about pulmonary oxygenation being absolutely a measure of lung function and lung function a measure of whether I live or die, I absolutely agree with you.

So having said that, I'm now going to defend a position that I'm going to offer, and Tom may help me word it correctly, because it's one that I
just still struggle a little bit with. The belief is that the best endpoints are ones that come as close as possible out of the patient's mouth in terms of their statement about how they feel, their statement about how they are functioning, and their visible evidence of not being dead. So feels, functions, and survives is the mantra. So how they say they feel, how they appear to function in terms of walking up and down the hall, those things are thought to be the highest order of good in terms of an endpoint.

So there's been a lot of weight -- so Tom Fleming, am I doing okay with that? So that's the reason why the committee has focused so hard on feels, functions, and survives, even though -- again, I'm with you on the need -- on the importance of the physiological parameters.

So you come down to CAP, and you think to yourself, well, what's my experience with people at around day 3 or day 4? If they tell me that they are feeling better, that my cough is better, my chest pain is better, and I'm eating lunch, it is
the case that -- I mean, there's probably some odd occasion when somebody's vital signs weren't actually better on that day, but I was, at least as a physician in the group, willing to say, if they're saying those things, probably that other stuff is better. And it dug us out of a real intellectual hole about the endpoint.

The clinical trials should also measure that stuff. So an important secondary measure for the clinical trial would be that, yes, your vital signs did improve. As a matter of fact, in the ceftaroline approval, part of the definition for that one was that there was an improvement in some critical vital signs; so stabilization as per the IDSA/ATS guidelines.

So it will not be ignored, but for purposes of digging us out of a hole -- and the hole we've fallen into is that we are looking for data that provides an adequate justification so that everybody can agree that we've got a way to do a non-inferiority study. That's the hole we fell into. And in order to dig out of it, we have
agreed that there's a little bit of connect-the-dots. The Bullowa data was mostly about fever, if you look at those.

Is Mary Singer in the room -- somebody can quote it. But, anyway, it's mostly about fever. Right? So that great graph that you put up -- I'm looking at Sumati Nambiar -- the graph that shows that the people who don't get an antibiotic remain ill for 10 days, and the people who do get an antibiotic, they actually improve dramatically, that's mostly about fever, right?

DR. NAMBIAR: Yes. I think it's defined as clinical response, which is primarily driven by fever, but included improvement in respiratory rate, heart rate, sort of a general improvement in toxemia.

DR. REX: So we took that as a measure that sort of all the dots are connected. And if the patient says they feel better, their fever is probably better, their vital signs are probably better. You don't sit up and eat lunch if you're not oxygenating more comfortably.
So it makes your head hurt, and it's really hard to wrap your head around. I have to agree with you. But that's the logic that went into it.

To Matt Goetz, does that answer your question as well?

DR. GOETZ: Well, I fundamentally agree that the most important question I ask a patient on day 3 is how are you feeling.

DR. REX: Yes.

DR. GOETZ: If they talk to me more than they did on day zero, I feel very comfortable I'm on the right pathway. But having said that -- my head hurts as well because I'm fundamentally a quantitative person, I think. So it comes back to, can we standardize those measures to everyone's satisfaction? And that's an operational detail, but an important one, of course.

DR. REX: May I speak to that as well? Because the FNIH committee talked about it.

DR. MOORE: Quickly.

DR. REX: The data that you're seeing in the FNIH analysis was drawn from studies where,
basically, what they put out was a scale of absent, mild, moderate, severe, and kind of left it up to people to define what that meant. So there's some wording in the protocol about this, but whatever wording it is, you could make up equally good wording. And there has not been a study that shows that my mild is your mild in Spanish, Vietnamese, and English. So understand, those data do not exist. And those data may never exist in a way that is compelling. It's important to recognize.

So another one of the simplifications the committee was willing to entertain was the concept that, at least over a very short period of time, if somebody says that they feel better, if they say, well, yesterday, it's awful and today, it's moderate, I'm willing to believe that they can probably remember that from yesterday.

So we accepted the notion that if I said, about myself, that yesterday I was severe and today it was moderate, I'm probably able -- that's actually probably a meaningful change. I mean, contrast that with rheumatoid arthritis, where
you've got it for 15 years. If I wanted to know how did my knee feel two years ago, how good am I at remembering that? And that's a place where a well-tested PRO was thought to be very valuable. But we felt like here we could make the simplifying assumption that we didn't have to have that because it was so short a duration.

Now, Mike Neely asked a question about altered mental status. We kind of didn't get into that. And so there's a point at which there is a gap, and I'm just going to acknowledge that there is a gap. And we may never actually span this gap.

I guess I will say that it was felt like this scale was good because it was as close to the patient words as we could get. It's like a physician-recorded patient-reported outcome. I mean, the doc has to kind of get it out of the patient and write it down. But the idea was, it was pretty close to the patient's sense of it.

Tom, do you want to say anything to this? Am I getting close to the sense of it?

DR. MOORE: Actually, Dr. Masur's been
waiting for a while to ask his question. I want to
make sure we get it in.

DR. REX: It's hard one. This is really
hard, though. We spent a year on this.

DR. MASUR: You wanted to respond to it?

DR. MOORE: Sure. That would be fine.

Okay, Dr. Fleming, go ahead.

DR. FLEMING: So let me try to just continue
on what John's laid out. First of all, to go back
to IOM, when IOM defined the measures, defined the
clinically relevant outcome measures under feels,
functions, and survives, they didn't create all of
this. I think that terminology actually goes back
to Bob Temple and FDA. And many others have been
evolving the thinking about measures for a long
time.

When they were saying functioning, they
weren't thinking about your biological functioning.
They were thinking about, can you carry out normal
activities. What are the tangible ways that a
patient would characterize whether or not we're
addressing what we care about?
So in this setting, clearly, survival in pneumonia is one of the tangible, but it's not the only one. If we say fever from the perspective of warmth and chills, which by the way, is not that strongly correlated with fever from the perspective of temperature, chest pain, breathlessness, coughs, sputum production, these are all measures beyond just survival that reflect important tangible ways that we can benefit patients in how they feel and function, in addition to surviving.

So, ideally, the measures that we would use to assess whether a treatment is truly benefitting what a patient cares about would be either direct measures of feels, functions, survives, or other measures that are properly validated.

Now, what are some of those other measures? Biomarkers. Well, how is a biomarker defined? And this is the IOM definition, but, by the way, again, it parallels much of what is in the regs with FDA and others. It's a measurement of biological processes, including physiological measurements, blood tests, other chemical analyses of tissue and
bodily fluids, genetic and metabolic data, measurements from images. So, clearly, they would characterize here, signs are biomarkers; radiologic exam, white blood count, temperature are biomarkers.

Now, those aren't useless. Those are very, very useful. Biomarkers have many separate kinds of uses. They're useful for detection of disease. They're useful for assessment of prognosis. If you have prostate cancer, rising PSA, while it isn't the clinical endpoint, can be useful for diagnosis and assessment of prognosis. Temperature could be useful for a clinician in guiding how you manage a patient. That's a useful way of using a biomarker, or for enrichment, identifying the kinds of patients that are most likely to benefit.

Complicated, though, is can we use it as an endpoint? Can we use it as the way to judge whether we're benefiting what a patient cares about? Answer, if it's properly validated, if there's evidence; not if it's a correlate, not if somebody who has response lives longer, but an
induction of an effect on response is evidence why, is shown to improve what people clinically care about.

To come to what was said, to clarify what was said, when we talk about temperature, the kinds of biomarkers that are more likely to be adequately, eventually validated as measures that when you show an effect on them, they show clinical benefit, are those that are the principal causal pathway for how the disease influences outcome.

So in a hypertensive setting, it probably is directly the principal causal pathway, that when you elevate your blood pressure, you're going to be at greater risk for stroke; or if you have an HIV infection, the viral load, the presence of the virus, is in fact not the endpoint patients care about. They care about AIDS-defining symptoms and death. But it's the principal causal pathway.

The point that was made is, in pneumonia, patients aren't, in fact, specifically at risk for and experiencing the symptoms and mortality because their temperature rises. In fact, some could argue
rising temperature is part of a physiological
response that's a normal healthy process to
affecting the outcome.

So it just argues that it actually becomes
an implausible candidate for an eventual,
effective, replacement endpoint, but it doesn't
invalidate what you're saying. What you're saying
is I would still use it clinically as I manage a
patient. That's fine. Nothing is being said
against that. It's saying, however, do we use that
measure to represent treatment effect when we're
looking eventually in an FDA setting of do we have
substantial evidence of efficacy.

That's what's led the FNIH group and many
others, as John Rex was indicating, to say, what
are measures that are direct measures of functions,
feels, and survives? What are the symptoms? And
John has listed those symptoms, and assessing them
at a time when we can set up an NI margin. We've
got evidence that in day 3 to 5, there's a big
effect of antibiotics on those symptoms. So we
have a direct measure of what functions, feels, and
survives, and we can set up an NI margin.

DR. MOORE: Dr. Masur, do you still remember your original question?

DR. MASUR: Well, it's probably been now beaten to death by everybody. The question is -- I agree with what Bill said. It's a little bit counterintuitive for us to move away from physiologic parameters because we're all much more comfortable with numbers. Yet, at the same time, in clinical trials, I'm never sure what to do with blood pressure, pulse, temperature, because without knowing what the baseline is and without knowing what the co-morbidity is, especially if we're looking at a population that's enriched for patients over 65 or with more severe disease, I'm not quite sure how to interpret that, especially given the variability in hospital settings of how these are measured.

If you're in ICU and you have a urinary thermoster [sic] and you have an arterial line, you can be pretty sure that you're getting regular measurements by the same techniques. If you're in
many settings, though, temperatures are measured by
a variety of different people with a variety of
different devices. Blood pressures are measured in
a number of ways. The question is, when you don't
know the baseline and you don't know the co-
morbidities, is that really a valid way of
evaluating the effect of your antibiotic on
pneumonia?

So I would share Bill’s discomfort in not
using them. I just have never found that they are
easy to interpret in these clinical trials. I'd be
interested if somebody has been more successful in
using these physiological parameters. So the
question is, are we putting to bed, in terms of our
opinion, the issue of using physiologic parameters,
rather than what John and Tom have been moving
towards?

DR. MOORE: Thanks.

Dr. D'Agostino, you're next.

DR. D'AGOSTINO: I wanted to make two
comments. One is on this, about the endpoints.
I'm nagged by the fact that I don't see a
standardization being mentioned. Maybe there is and it's not being laid out here, but I'd like to see that. The other one, which is my original question, is the ITT versus the per-protocol analysis.

The ITT is as randomized as the groups and so forth, so I've always felt much more comfortable with that being an analysis population. And I understand that that can in fact have an effect on bringing the groups together and one has to be worried about that.

But what was the logic, or is there a logic, in terms of it being presented to us as only the ITT? Is it implicit that there's going to be also per-protocol, and there must be a matching of the two, and the ITT is somehow or other the primary; or is it saying it is the ITT analysis that wins the day and it's the sole one?

So I'd like to hear Dean and Tom, who might have some discussion on that.

DR. FOLLMANN: I guess I just have a standard view about this. And just to clarify
things to start with, we're using ITT and also microbiologic ITT. To me, I lean more towards the microbiological ITT or the micro-ITT, as the main analysis that will be what will be focused on. I'm sort of showing my hand as to how I view the next questions.

   But, anyway, I think the standard view that I have on that is that you want to look at both, in this instance, the micro-ITT as well as the as-treated amongst those in the micro-ITT, and look for concordance, and so on.

   When push comes to shove, I guess I would focus my attentions on the micro-ITT and just look for concordance with the as-treated micro-ITT analysis, just as we would look for concordance with the later endpoint, sort of the cure kind of endpoint, that will be secondary, and something that we'll look to be concordant with the 3- to 5-day endpoint.

   So that's my view on this as-treated thing. I think in the documents we've seen, it hasn't really been discussed very much at all here. It
was sort of absent, and I guess -- anyway, that's my view about it.

DR. D'AGOSTINO: I can imagine in a test like this that there'd be a lot of individuals who were not treated sort of appropriately or what have you, and so the ITT population could be banged all over the place; is that the experience or is that not --

DR. FOLLMANN: You know, we've seen data that shows just a little prior antibiotics seems to have an effect, so how much banging is, you know, maybe missing a bit, going to do, anyway.

DR. MOORE: We have several questions in the queue. Dr. Fratzke?

DR. FRATZKE: I just want to comment because I have experienced the things you're talking about here today. And I've been in the hospital and was diagnosed. I actually ended up with a bacterial and viral combination, and even suspected fungal.

So I'd look at this -- one of the things we talked about today was the diagnosis that occurred at the very start, the rapid diagnosis. And I also
want to comment on the patient's response to success, because once they found out what the organisms were that were affecting me, I knew by day 4, this was a huge improvement. So no question, I think the patient's response is very important in the success determination.

DR. MOORE: Dr. Reller?

Thank you, Dr. Fratzke.

DR. RELLER: I understand the emphasis on feels, functions, and survives, the last one of which, clearly, is pretty objective. But I'm a bit troubled by possible fuzziness in some of the other symptom endpoints.

With that viral co-infection, maybe the cough's worse at day 3 or 4, but it doesn't mean that things are going to go okay. Those symptoms may be direct, but to some degree, some more than others, are imprecise.

I'm troubled by discounting the signs altogether. It seems to me they're complementary and they serve different possible purposes. The signs, depending on one's viewpoint, may be more
indirect; but done reasonably well, they tend to be more objective, so one has to balance between these two features. So I have questions for panel members.

First, Dr. Masur, I agree with everything you said about the signs, except that if one enrolls a patient and the white count's 25,000, temperature is 103, et cetera, one of the options posed to us, option 2, is that they would become normal or would proceed toward normal by days 3 to 5, or stabilize.

If one has abnormal signs at the outset in a patient with other criteria for pneumonia, wouldn't you expect that one could observe a change toward normal if things are going well? And I'll give the example of, if on day 3 or 4, the patient may -- on that day, sometimes how patients feel is a little bit like the stock market. It goes up on any given day. There's a trend over time.

But if on day 3 or 4, the white count is still 22,000, 23,000, and the temperature is still 102, that tells me that there's trouble somewhere.
I may not know it. Maybe there is a pleural effusion, go back -- maybe tomorrow we're going to need a chest tube for -- I mean, I just am -- it bothers me that we cast out what has been, from a clinical perspective, if one wants the clinical trials to reflect -- as been mentioned by several -- to the extent possible, we want to be objective, but we want to have it in concert with clinical practice if possible.

This divorcing of signs and symptoms bothers me a bit. Now, we could argue about which ones should be included. And as Dean, I've sort of revealed my hand.

So if you could comment on that. And then the other question that I'd like commented on is to clarify, again, what the statistical roadblocks, implications, impasses would be with some combination of symptoms and signs as a primary endpoint. I understood about you can't do it one way, and then in another time period, combine things because that doesn't work that way. You minimize differences, if I understood correctly.
But if at the outset said this is our primary endpoint and then we're going to have to have -- those will have to be maintained out at a later time, does that pose a problem?

So those are the two questions that would help me a lot in how I come down on this eventually.

DR. MOORE: Dr. Masur?

DR. MASUR: I would hope that no one in this room would deny that using clinical parameters is useful for clinical management. I certainly agree with that. The question is, in the study, can you collect those data in a consistent way? I mean, if we could get temperatures -- maybe at Duke they get temperatures four times a day on every patient. We have trouble sometimes getting it more than a couple times. But if you can get reliable temperatures, that's probably easier to manage than, say, blood pressure, where there's a big difference in terms of what the baseline is.

Clinically, certainly, we all know that if the patient has a blood pressure of 70 and they
came in at 110, we know what to make of it. But the problem is just, hypotension is relative. But if in these trials you could get temperatures measured reliably on a regular basis and then have some definition of whether you're going to use a peak, that would be fine to use. My experience has just been that in a trial, that's difficult. But clinically, I would certainly not want to maintain that you don't use these regularly, and you'd be remiss if you don't.

DR. MOORE: Dr. Neely?

DR. NEELY: Just to follow up on that, the other slight problem I see with the vital signs is that we do things as physicians to normalize them. So for fever, we give antipyretics. For tachycardia, we give fluids. For hypotension, we also give fluids. So I think that also can confound it.

I like the idea of focusing on how the patient feels, but as I raised earlier, I do think we need to make or solicit some effort to try to standardized that. And that's been well done in
many other areas. There are the pain scores, both in adults and certainly in children, visual analog scales. I mean, it's I think quite well validated that we can, in some way, objectify these subjective criteria.

DR. MOORE: Just a word about that. I guess I would say that we give antipyretics. That's agreed. But we give antipyretics in response to the fever. It's not normal that we give antipyretics around the clock, and, thus, block the ability to generate a fever; similarly, the beta blockers.

DR. NEELY: Maybe that's a different practice, then, in the adult world. In pediatrics, we sometimes, not infrequently, will give it round-the-clock, if the patient is having round-the-clock fevers.

DR. MOORE: There you go. Okay. That's why you're on the panel. Thank you.

Let's go with Dr. Temple.

DR. TEMPLE: I don't want to sound too obsessive about this, and I'm sorry I don't have
anything to say about fever. The two analyses that are being talked about, ITT and -- are missing the main point. The microbial analysis is, in fact, a subset analysis. That's what it is. And subset analyses are fine. And the overall analysis is expected, of everybody, not to be as precise because some of those people may or may not have the disease. So it's an enrichment design, using a subset analysis, which is perfectly appropriate.

The second question is whether you really want to do an ITT analysis or focus on the people more likely to be able to show you a difference. I think it's fairly obvious that, in most non-inferiority studies, you want to look on the as-treated people; at least as a primary analysis, you can look at the other two. And I think that needs some resolution and discussion. You don't want someone who only got a day of treatment. They won't show a difference between the treatments, even if the treatments are markedly different. ITT minimizes differences. We accept it in different showing trials because we want to be conservative,
and we don't want informative censoring, and all that stuff. But it has a bad property, and that is, it tends to make the differences between treatments smaller, which is absolutely not what you want here.

So I think the terminology and what we're talking about needs some attention, and Ralph and Tom ought to comment.

DR. D'AGOSTINO: Can I comment?

I think that what I'm finding in the whole discussion is that I'm uncomfortable with the lack of rigor, in terms of how you operationalize this, the question about the symptoms. How do you take that measurement so they're standardized? I know we say you take them, but how do you take them so they're standardized? I don't see that.

The same with the discussion on the ITT versus the per-protocol; I have no problem with them jumping to the micro and saying that they'd like to see how that works out, but you're going to have to look at everything -- you're going to have to look at the full analysis -- look at the full
group of individuals, and then do you trim it down
to a per-protocol and ITT.

I don't hear -- and I don't have the
experience with these particular trials on what
trouble you have, but in other things where I've
done non-inferiority trials, the per-protocol, not
that I want it to be the primary, is the one that I
feel most comfortable with in terms of
understanding what the data is actually telling me.
And I want the ITT to do the same, and show me the
same, because, again, it's the one that's the
randomization and so forth.

But I don't see this sort of level of rigor
in terms of our discussion. How do we know that
the ITT isn't going to create problems such as
treatment for a day and things of that nature? And
do we have a lot of experience? And you've gone
through this for three or four years, so you
probably do, in terms of what these studies
actually look like.

But I find, just to cap the discussion, that
this sort of rigor that I think of being imposed in
other trials, I don't see here in terms of what the
definitions are, what's going on with the ITT
versus per-protocol, as another example.

DR. MOORE: Dr. Wiedermann, you had a
question or point?

DR. WIEDERMANN: Really, more of a comment.
I'm not as -- you know, there's always a tension
here between clinicians and statisticians, almost
about anything we discuss at these kinds of
meetings. I'm actually a clinician who likes
statistics, strangely enough.

[Laughter.]

DR. MOORE: It's an amicable difference. I
guess I'll put it that way.

DR. WIEDERMANN: There's probably only one
thing I hate more than a non-inferiority trial, and
that's being painted into a corner by antibiotic-
resistant bacteria and running out of choices. So
I've already gone through my Kubler Ross stages of
mourning, and we're going to have a non-inferiority
trial, and we need to do it because we need more
options for the future to treat pneumonia and many
other things.

Having said that, to me, the endpoint is not like just anybody's going to throw away data or not collect data on these patients. To me, the purpose of the endpoint is to do a sample size determination and make sure you're not setting yourself up for total failure and no conclusions at the end.

So my head doesn't hurt and I'm not bothered as much by all of these hand-wringing things. I'm really looking -- if you look at Dr. Laessig's presentation, I'm looking at the options and then I'm looking at the sample size. And I'm trying to figure out what's the balance. You have to give up the least amount of rigor in the study design, but not so strict that you make it an impossible study in geologic time, as Dr. Rex I think said.

So to me, I worry less about the arguments over fever and things like that because we'll still have that. It's up to the investigators and journal editors to make sure that piece comes out and it's explained in the study report.
DR. MOORE: Dr. Bennett?

DR. BENNETT: I want to turn our attention back to the microbiologically proven category because I'm not sure that it's proven as well as the term might imply. We're all aware that people will cough up pneumococci when they don't have disease, but people with chronic obstructive disease, pulmonary disease who are well prone to getting pneumonia, also cough up haemophilus species and moraxella, which has no clinical significance.

In addition, there's the issue about the viruses, which we've already discussed, but in the hospital where Henry and I work, we end up doing nasopharyngeal washes every week so we can find out when to take a person off isolation who's been coughing up a viral influenza or a parainfluenza type 3. And what we've discovered is they continue to cough it up; we're having their washes for weeks. Now, maybe that's just our patients, but I doubt that. It's just, how many outpatients do you culture every week like we do?
So what we're faced with in clinical trial, in clinical experience there, is we'll have a person who's been carrying, let's say, a paraflu for the last four weeks; now they have pneumonia. What does that have to do with anything? Maybe absolutely nothing. So although we call it microbiologically proven, I'm not as sanguine as to how proven they are.

DR. MOORE: Very good.

Dr. Fleming?

DR. FLEMING: I'd like to add some brief comments to several points, including Dr. Reller's question. So as FNIH was approaching this, I think I can speak for the group to say they were trying to address several aspects and help move the field forward so that we would be in a position be able to continue in the near-term development of new antibiotics for CAP.

One of the aspects was, as we've already mentioned, coming up with a direct measure of functions, feels, and survives; that is the cough, breathlessness, chest pains, sputum production.
Another is to be able to have that measure, have an
evidence-based non-inferiority margin. And the
third is to be well-defined and reliable. And
several people have appropriately said there is
some uneasiness with the nature of the
subjectivity. And we can, in fact, take inherently
subjective measures, and make them defined and
standardized in how they're assessed, and
ultimately establish content validity for being
well-defined and reliable.

What the FNIH said is there are two steps
here. The first step was to come forward with this
proposal, recognizing that there are still
additional steps to the refinement of the
standardization, but we didn't want the three years
that's going to take to delay further the
development of antibiotics for CAP.

So the proposal was to go forward with this
measure that's close, but does in fact still have
need for better refinement while that refinement
work goes forward. And there's a stage 2 to FNIH,
as well as others in industry and elsewhere that
will continue to pursue that stage 2.

Second point is, I don't think anybody is saying we should ignore signs, or dismiss signs, or say this is only about symptoms. What's being stated is, the assessment of symptoms needs to be done separately from the assessment of signs.

Now, you asked a good point, Dr. Reller. What happens if you pool them? So the example that I was trying to give of what could happen if you pool them is, suppose you have a standard therapy that has only 15 percent of patients failing on resolution of symptoms, which patients directly care about, an experimental therapy that's twice as many, that has 30 percent of patients who fail, and yet in the standard therapy, there may be 15 percent of patients who resolve their system, but haven't fully resolved their temperature or their white blood count?

If you use a composite endpoint, bringing signs and symptoms in, then you have 30 percent failure in both arms. You missed the fact that, in fact, the experimental therapy has twice as many
patients failing on what patients directly care about.

So the idea isn't to ignore the signs. It's to assess them separately. And the question is, if you're assessing symptoms as a primary endpoint and then separately assessing signs -- you're not ignoring them -- do you also have to win on signs also, as a co-primary, or is it okay for it to be a supportive measure as a secondary endpoint, so that if you've won on the symptoms, you'll care about what happens on signs, but you may not necessarily also require a win on the signs?

The last point Dr. Temple was referring to, the per-protocol versus the ITT, and I like the way you characterized the micro-ITT is a subset analysis, and the focus on it is really important because it's an important subset, but less than 50 percent. I hope we can get it to be 40 percent. But if the non-micro-ITT is 60 percent and we have patients that in fact have a viral infection and don't in fact benefit from active therapy, they're going to dilute the sensitivity for your non-
inferiority analysis.

So, therefore, as Dr. Temple says, a critical question, then, is do we allow the enrollment -- because, as Dr. Bartlett says, it's difficult to prevent their enrollment -- but have a pre-specified analysis that focuses on those that are sensitive, the micro-ITT subgroup analysis, as Dr. Temple says?

Separate point, valid one, separate point; whichever you do, ITT or micro-ITT, should you do the per-protocol rather than the ITT? I think many of us think you do both on that point. You look at both of them. And, fortunately, with a day-4 primary endpoint, the difference between a per-protocol and an ITT will be less on a day-4 endpoint.

So it's not that your point is being ignored; it's there. But the more profound point here is, do you exclude the 60 percent who aren't the micro-ITT? And that's why that's gotten more focus in this discussion, not because that issue you've raised, Bob, isn't important, too.
DR. MOORE: I think we've had plenty discussion on question 1. Of course, thankfully, it spilled over to question 2 and 3 as well.

Yes, Dr. Reller?

DR. RELLER: Tom, until one knows how well these things perform, is there any rationale for having, for example, a co-primary endpoint, but having a different margin of non-inferiority for one set of values and the other set of values?

DR. MOORE: Dr. Fleming?

DR. FLEMING: That could certainly be done. To me, the critical point, Dr. Reller, is that we do have a separate assessment of those two domains. And I believe I can say the FNIH approach was to say, at this point, what establishes efficacy is the ability to rule out.

We can do a non-inferiority margin on that measure of symptom resolution, but we don't ignore; we also give attention to. And it's up to this group to define, is the attention you want to give to symptoms one that's a supportive measure, that if things are going badly, you'll be alerted by, or
do you actually want to require that if you fully
resolve symptoms and you haven't quite fully
resolved temperature and white blood count, that we
don't want to approve that antibiotic?

You're getting my personal view of this.
I'd want to approve that antibiotic. But if you
wish to have another criterion that would say, you
also have to resolve signs, I would agree with you
if you say that it should have its own margin.

DR. MOORE: Dr. Rex and then Dr. Calhoun.

DR. REX: So I'd like to try to weave
together sort of a summary of what I've heard over
the last few minutes, because I really do want to
reflect on the fact that the clinicians in the
room are saying that the elements that comprise the
traditional test of cure are highly desirable in
our analyses and are part of standard care.
Staying on the initial antibiotic or being analyzed
as treated, initial improvement followed by
ultimate resolution. Okay? Those are things that
we all really want.

Let me say to the clinicians in the room, I
absolutely agree with you. Indeed, I agree, a
hundred percent. And if you read the FNIH
document, you'll find a section, Section 3.2,
entitled, Alternate Viewpoints: Issues,
Limitations, and Areas for Future Work, that was
inserted, in large part, at my behest because I did
not want the FNIH document to go on the record with
it saying that we all gathered around and agreed a
hundred percent that this new approach was perfect.
It is not.

Very important, there's a critical
limitation about it. This section talks about the
fact that the traditional test-of-cure endpoint
works, has worked historically, just fine with
sufficiently ill patients because it implicitly
includes the early endpoint.

Now, you can enroll patients who are so
mildly ill -- and we saw some examples of that this
morning -- that you can't ever measure anything.
You measure sick enough people, that endpoint is
always there, and it has to be there in every study
of every infection. But the core problem -- and
this is the one to be aware of as you talk about it -- is that we've been unable to agree that we have adequate data for a non-inferiority margin, and that has been killing industry. No one's been able to do trials. The entire industry is in disarray because it has looked like you couldn't work in this area.

The debates have raged -- and some of you have been at those debates -- over whether or not we have adequate data to set a margin. I don't want to reopen that debate. We are going to actually have to tackle it tomorrow, in earnest, in an area where we have less data, and it certainly makes my head hurt. I won't speak for anybody else, but let's save that for tomorrow.

So you're now seeing the results of many years. And some of you are response for this, so there you go. But, fortunately, we do have this way out of the hole. The FNIH suggestion seems close enough to clinical reality to work. It seems acceptable to all the debating partners. And, critically, it will allow the industry to get
moving. And if we don't do that, CAP development in the United States is over. It's going to be the end. It may be the end elsewhere, but it certainly won't happen in the United States if we don't get out of this hole. That's going to be the end of it. So it's critical that we have something that gets us moving.

I guess I'll put my nickel's worth on the table. The three designs that Katie Laessig took us through, I think they're all fine. Each one of them has a strength and has a weakness. And I would actually like to see all of them made available, because let me emphasize how little experience we have with this new endpoint. Are you ready to know how much we have? Does the number zero mean anything?

That's how much prospective experience we have. We have used these endpoints, retrospectively, based on some datasets. We hope we're right, but the next few sponsors are going to be guinea pigs for this. Biologically, the endpoints make a lot of good sense. It feels like
it ought to be pretty good. But precisely how it's going to play out, I don't know.

So I hope this committee remembers that when it comes to reviewing data using these endpoints in a few years, if somebody's brave enough to put their money on the table and do the study.

There is one thing that I do have to raise for the record, and it's about there is an additional way out of this hole that is being largely ignored. David Shlaes alluded to it. It was a code word. The word was "pharmacometrics." He put it on his slide and he says, "What about pharmacometrics?"

Pharmacometrics is the approach of using the observed blood levels in patients from clinical trials and turning those into a pharmacodynamic estimator, looking at the correlation between MIC, plasma exposure, and outcome, and using that to -- when you do that, what you find is that, surprise, surprise, as blood levels go down and as MIC goes up, the patients do worse. And you can actually estimate that back to zero and estimate
the treatment effect size for any endpoints you
care to define.

So it is possible to define a more
traditional-looking endpoint using pharmacometrics,
and get an estimate of the treatment effect size,
and get an estimate of non-inferiority margin.
Having said that, I will also say there are
critiques of that, but those are laid out,
carefully written, in the FNIH document.

But I think it's worth seriously considering
whether some elements of that could be used, going
forward. And I would encourage the FDA's document,
the final document, to provide an option for
somebody to develop a response along those lines.
Thank you.

DR. MOORE: I'm going to go with Dr. Calhoun, and then I think we should really go
around the table and have everybody commit.

DR. CALHOUN: Thanks. These are overarching
questions, one conceptual and one technical. And
they both actually turn on the biostat. The first
conceptual issue is that patients are different.
There's patient heterogeneity in responses. We haven't really talked about that today. So of the symptoms that are listed here, cough, sputum production, chest pain, difficulty breathing, et cetera, et cetera, even given the same microbiology, patients may have different expressions of that.

The biostat question I've got for you, Drs. Fleming and D'Agostino, would be exactly the same objection that you raised, legitimately I think, with respect to bundling composite endpoints together. But if we've got four symptoms, and we put those all together, and a given patient only has one or two of those, that will, in fact, bias to the null, right? Because there won't be any symptoms in those other channels.

Let's say they just have cough, and they don't have sputum production, and they don't have chest pain -- I mean, that's, perhaps, common. So the conceptual issue is what do we do about the heterogeneity of expression of what might be microbiologically identical disease? Pneumococcal
pneumonia doesn't get expressed in everyone the same way. And I've got a technical question I'd like to ask.

DR. MOORE: Dean, do you want to handle that?

DR. FOLLmann: I just wanted to comment on that. For me, implicitly, the endpoint is improvement on two of four symptoms. So if you enroll a patient who has no symptoms, that should be basically an exclusion criteria. So I thought, implicitly, you would have to have someone who had a reasonable expectation of being able to meet the endpoint. So that means, I would think, you'd have to have at least two of the symptoms, maybe three, as an inclusion criteria.

DR. MOORE: Dr. Fleming?

DR. FLEMING: Indeed and in fact, when FNIH looked through the data, one of the important findings was that, John, it's well above 90, 94 percent, or some high fraction of the patients, did in fact have at least two symptoms at baseline.

DR. REX: Yes. It was, easily. I think 94
is the number. Really, most folks, you're not
going to lose a lot by requiring two symptoms.

DR. FLEMING: And then the other part of
your point is also correct. And that is, you note
that when you have a certain physiologic
measurement, that how that plays out in patients in
terms of what their symptomatology is could be
quite variable. But therein lies, in fact, part of
the disconnect between them being able to say, if I
affect that physiologic measure, I'll reliably be
predicting I'm going to affect what's tangible to
patients.

DR. CALHOUN: So the technical question,
again, for the biostat guys is, I think we had
talked at one of our prior meetings about using a
proportional reduction in risk as opposed to an
absolute number for a non-inferiority margin, and
we didn't talk about that at all today.

I mean, I can imagine that if you've got an
effect size that's 10 percent, 70 to 80, that
losing a piece of that is -- losing 5 percent of
that is a smaller deal than if you've got an effect
size that's 20 to 30 and you lose five points on that.

DR. MOORE: Yes, Dr. Fleming?

DR. FLEMING: Very important point, and it will be key tomorrow. So, in fact, if you said I wanted to have a margin of absolute difference of 10 percent, that could readily be an appropriate evidence-based margin when you have an 80 percent success rate.

Basically, you're saying, I want to rule out that their 20 percent failures become 30 percent failures. But if you were to put a population on where the success rate is 98 percent, then it's harder to justify. Particularly if this were a mortality endpoint -- tomorrow -- it would be harder to justify that same absolute difference would be appropriate, but that a relative-increase measure could still be appropriate.

One of the problems in our setting with CAP -- and we thought a lot about this in characterizing the measures -- was that if you had an endpoint that was 98 percent, successful in a
control, it's subtly or not so subtly tempting to put patients on where almost everybody is going to be a success, and you're calling everybody a success. And you're going to have lack of sensitivity to an agent that's less effective. That's addressed by your recognition that if you did it as an odds-ratio approach, that gets around that problem.

Fortunately, I think our sense is, from the evidence that we have here, that there will be an 80 percent, but, hence, 20 percent failure rate. I think we can go about this with absolute differences with margins. But tomorrow, this will be an issue.

DR. MOORE: Let me stop you.

DR. D'AGOSTINO: May I comment on that?

DR. MOORE: Yes.

DR. D'AGOSTINO: I think that's a very important question. When I got the material, I was going crazy trying to say, well, why are they sticking to the difference? Because, quite often, in the arenas I'm dealing with, you're talking
about relative risk reductions. The risk itself is very small. And here you're dealing with things like 80 percent; 20 percent if you want to look at the complement of it. And there putting absolute usually turns out not to be a problem.

If you get so good in generating these medications, you're going to be wandering into the problem that you're talking about, where the rates will be very high. And then you're going to have to switch the metric, I think, in order to really get a sense of improvements.

DR. MOORE: Thank you.

Okay. With that, I think we're going to stop the discussion. We're going to go around the table now, and I will start with you, Dr. Reller, if you could. A lot of us have had our say, but I want to make sure those of you who haven't spoken have your say. But we're just going to go in an orderly fashion, from left to right. If you could, just say what's on your mind --

[Laughter.]

DR. MOORE: -- that you have or haven't said
already.

DR. RELLER: Well, of the options proposed, I favor two. I don't like what three looks like, and I'd be -- if I were negotiating, I'd be willing to consider 1, but I really like 2. And I understand about the separate analyses. And if there were statistical help on -- it's sort of implied in 3 that there might be a difference in resolution of signs, depending on how many you require; I mean at least two on the symptoms. If it's two on the signs, then which signs would be included, and then the option is for having two of those.

But that there's 80 percent success rate on one and seven in the other implies, to me at least, that there might be some difference. So then it would be getting help from colleagues as to what might be appropriate differences for the margin required for non-inferiority.

Any way one goes about it, this is a great change from mortality-only endpoints.

DR. MOORE: Thank you. Dr. Roberts?
DR. ROBERTS: Yes. I think the options are fine. I would certainly endorse Dr. Rex's endorsement of the pharmacometrics as an adjunct, speaking from a clinician side.

DR. MOORE: Thanks. Dr. Fleming?

DR. FLEMING: In December of '09, as this committee last considered what we could be doing going forward, mortality with an evidence-based margin was put forward as an option, but there were many concerns expressed about the feasibility of using that approach. There was much discussion about clinical response at test of cure.

Part of the problem with that is the lack of an evidence-based margin, as John has talked about. But part of the problem also is, it's a measure that is not well-defined and reliable. It's a measure that's mixing signs and symptoms. And the interpretability of that, from the perspective of how you're influencing what's tangible to patients, was difficult to interpret.

I am very impressed with a lot of effort that many people have expended in 2010 and 2011 to
try to move forward beyond an option that would
simply be mortality. The option that's laid out
here in this discussion is one that, in fact, does
focus on a measure of functions, feels, and
survives, not to the exclusion of signs as other
endpoints, but a functions, feels, survives
measure, one that's better defined, one that's
sensitive to what patients care about, one that's
sensitive to where the treatment effects are really
likely to be the greatest. Its limitation, as is
noted, is future research is going to be needed to
get better standardization and better content
validity for how this is assessed.

So, in essence, my sense is, it gives us an
option to move forward beyond a mortality endpoint,
while further refinement of this thinking goes on.

FNIH did not spend time talking about the
non-inferiority margin. The sense of the group,
though, was that this is a measure for which there
is good evidence of real benefit. The Finland
article that was shown, that had figure 2, presents
fairly direct evidence -- now, it's not randomized,
but fairly direct evidence -- showing, for example, that I think, 72 hours or 48 hours, the difference in success was 41 percent against 71 percent. But that 30 percent, just to do a quick calculation, was plus or minus 10 percent. The lower limit of that is 20.

So a confidence of 20, and if the traditional approach for NI margins is preserving half the effect, it would argue for a 10 percent margin.

As I think Ralph said, that's pretty loose reasoning compared to what we do and how we define margins in other settings. But, to me, I would be comfortable accepting that 10 percent margin for the primary analysis of the micro-ITT. If a bigger margin would be appropriate, I'd be very interested to hear what the evidence-based rationale for that would be, but I think we could go to the evidence that Finland's put forward to say we can justify using this measure with a 10 percent margin.

DR. MOORE: Thank you. Dr. Fratzke, our patient representative.
DR. FRATZKE: I'd just like to add one thing. I mentioned about the subjective patient response. And I have realized -- I agree, people have different reactions and responses, and as a dentist, pain was one. Someone would say this doesn't hurt and it should be, and another person would just have different reactions.

So it is tough. So I think it's real hard for us to get a standardization for the subjective thought of the patient, but I hope they can do it.

DR. MOORE: Thank you. Dr. Goetz?

DR. GOETZ: The discussion has been extremely illuminating and drives me to the conclusion that the symptom-based measurement with improvement of two of the four categories will be satisfactory and will do a large part to capture the Gestalt of how the patient feels.

Clearly, there's more work that needs to be done to validate, to better understand, to standardize, to increase everyone's confidence. But I also do fundamentally believe that while we may not all score the same -- five of us looking at
the same patient may score moderate, mild, and severe -- and I could change my mind at different hours of the day as to how I scored the same response on the patient -- we're probably better, and the patient's better by reporting direction of change, which is fundamentally more important than when a person goes from severe to moderate or moderate to mild; it's the directionality, which is the key part of that, as I see it.

So I've been driven by the discussion to change my perspective that I came in with today.

Insofar as the other question, for question 1, is sort of the non-inferiority margin, it is fuzzy math, so to speak. And fundamentally, I'd like smaller non-inferiority margins, because as has been oftentimes pointed out, the wider the non-inferiority margin is, the greater the opportunity to saying something is non-inferior that truly is inferior. At the same time, feasibility is a very important issue. And if we wind up with sample sizes that industry has no motivation to go forward, well, truly, the perfect
has become the enemy of the good.

That's a sort of preface to my saying that I also think that the risk that's engaged depends upon what the outcome is. Increases in mortality are much more riveting than increases in, "I don't feel quite as well on day 3," but are ultimately cured.

So from that perspective, although the math is fuzzy, I think that 10 percent may be a more rigorous margin that is warranted, and that kind of leads me to 12 and a half, but I must admit that this is not a place where any of us can put down the 10th decimal point with any confidence.

DR. MOORE: Thank you. Dr. Neely?

DR. NEELY: I think I've already made my point about trying to objectify the subjective criteria as much as possible. I do have one even more fundamental point that underlies question 1, in that I think we need to be clear, perhaps, in an effort to encourage industry to develop antibiotics for the treatment of pneumonia. And when I say pneumonia, I'm not just restricting it to
community-acquired.

By definition, for a non-inferiority trial, we're trying to prove that the innovator drug is not inferior to the standard therapy. Well, with ceftriaxone, we have a drug that has a 2.8 percent mortality. It's cheap. It's once a day. So where is the a priori benefit in the innovator drug for a non-inferiority trial? If we're going to say from the outset we assume or we're looking to prove that it's not inferior, there has to be some other benefit besides efficacy that we're looking for, for this drug.

So why are we doing a study for this innovator drug for community-acquired pneumonia? I think we're going to have a very different discussion tomorrow because the money, from my standpoint, with the exception of MRSA for community-acquired MRSA, is in treating resistant Gram negatives, which, at least in the pediatric world -- I don't know so much in the adult world -- we're not seeing in community-acquired pneumonia.
We are dealing with community-acquired MRSA, and that's where ceftaroline obviously has activity against MRSA in vitro. But for the label for community-acquired pneumonia, it's not labeled for the treatment of community-acquired pneumonia, whereas it is for the skin and soft tissue infections.

So where is the benefit for ceftaroline for community-acquired pneumonia if you just look at the package insert? So I guess we need to clearly delineate why we want studies to be done in community-acquired pneumonia. I guess it would be to protect for future development of resistance. But in that case, would we be able to extrapolate from hospital-acquired and ventilator-acquired pneumonia studies to resistant organisms in the community setting?

So I think there's some real fundamental issues here that need to be addressed.

DR. MOORE: Thank you. Dr. Follmann?

DR. FOLLMANN: So, as many people have mentioned, we've been at this for a very long time.
And I wanted to just say, I think it's really fortunate that we've been able to come up with an endpoint like this, that seems like it'll get us off the block that we've been on.

Some of the merits I see in this endpoint is, one, that we can have -- we can, based on the historical evidence, try to find an M1 that seems reasonable. This allows us to divine an M2. So it satisfies the very first thing we need in an endpoint, some historical evidence of a treatment effect. It's also nice, in my opinion, or necessary, really, because it reflects how patients feel and function, or survive.

Another benefit, in my point of view, which was made earlier, is that it's relatively early in the course, and so there's less risk of pollution with ancillary therapy and so on that you might get with at test-of-cure endpoint. And, also, there will be less chance -- there will be more harmony between the as-treated and the intention-to-treat analyses, because, presumably, there's less chance for people to fall off therapy or to have
complications come in.

So those I think are the main merits. And the biggest thing in my mind is that it's something we can work with and proceed with.

The limitation, the one thing that was articulated better than I could earlier was, there might be a compound that has anti-inflammatory and bacteriostatic effects. And so it looks kind of good early on, but then, later, perhaps it doesn't really pan out. And I think that's just something we have to be aware of. And I think, if such a compound were being tested, we'd be aware of that. And we can also always look at the consistency of the results between the 3- and the 5-day endpoint, and then something that's long term. And so, hopefully, that concerning situation would be flagged or identified at some point.

In terms of the margin, I think that, based on the historical evidence, we have reliable evidence of at least a 20 percent M1. And so if we have about an 80 percent success rate, I'm comfortable with a 10 percent margin.
Dr. Calhoun and others have pointed out -- and it's been a concern of mine -- that maybe this is not going to always be 80 percent success rate in the studies that we have done. Dr. Rex pointed out this is essentially a new endpoint. And I think as studies are done on this, we might find that the success rate differs. And we have to be aware of that. And I think this leads naturally to allowing margin calibration- or odds-ratio-type margins.

So when I read this, I thought, we'd want some kind of odds-ratio margin, truly, that calibrates to about 10 percent at an 80 percent success rate, which is what we've talked about. But it has to allow for some shift in that because we don't really know what's going to happen. And I think it's scary to have a fixed margin when the event rate can vary quite a lot from that. It can basically destroy the trial one way or the other. And in my mind, it's an unnecessary risk. It's something that we can protect against with sort of an odds-ratio kind of margin at the outset.
DR. MOORE: Thank you, Dr. Follmann.

This is Dr. Moore. Restricting my comments to question 1, what I'd say is I feel a little bit still lost in the statistical, well, in my mind, sort of morass of -- I mean, I get everybody's point that the signs will not be lost, but I still have trouble as a clinician not giving equal weight to clinical signs of disease, which are how we practice; that is, not just how the patient is feeling better.

I share Dr. Goetz's viewpoint that this discussion has changed my perspective on this item, and yet, somehow, it's just hard for me to divorce those two, because, to me, they're part and parcel of the same process.

So there are two issues here. I guess I would have to leave to the statisticians how those endpoints would be included and matched together with symptoms. I agree, symptoms should be the primary endpoint. But whether they should be a shared endpoint with signs or not, that's a question we'll deal with here in a few minutes.
What I would say is I support the inclusion of time to clinical stability as an endpoint, if that can be done, and also in terms of -- one thing that came up earlier was the question of using PORT scores versus CURB-65, or both, or just age. I feel the same as Dr. Bartlett. I don't really have a particular preference one way or the other; whatever would be easier. And certainly using CURB-65 or age would be easier, but getting more data is always attractive.

With regard to the non-inferiority margin of 10, 12 and a half, or 15 percent, this has come up with previous committee discussions, with the 10 percent margin and not increasing it much more or not increasing it further than that.

I guess I'll just leave it there.

Dr. Sepkowitz?

DR. SEPKOWITZ: So I'm pleased to be in a group that is picking subjective symptoms over objective signs. I think that's progress in its own perverse way. I think we do need to objectify the subjective, which is what Michael was saying.
But I think that we are all worried about the subjectiveness of the objective, if I may say, which is what Henry Masur was saying.

I think, usually, respiratory rates are absolutely fabricated. I think that blood pressure is normal as all over the place, and I think temperature can be masked too easily. And there are other causes of fever that are not related to the disease process. So I don't think that they are reliable, though they are objective. So I think that's kind of neat.

I have some concerns. FNIH, thank you for doing the work you did. I think it's worth noting that the FNIH's membership is overwhelmingly pharmaceutical, if I understand it, from page 33. And it's odd -- this is actually a criticism of the meeting -- that we didn't have a presentation of who they were and what their methods were. And yet we're asked to endorse, blindly, their findings.

The magic day 3 to 5 symptoms is derived from -- if I'm understanding it from page 31, from what you guys sent around to us -- several hundred
patients only. And it's the ti-levofloxacin study
that we didn't see any of the primary information
on.

So it's large buffet. I am a believer that
the day 3 to 5 makes a whole lot of sense, but I
think we're relying on a group that didn't present
the data primarily to us, nor provide it for us to
make that leap.

Do I have anything crankier to say? The
margin is way over my head. I think
feasibility -- I do want to say that I find it
ironic that, on the one hand, we have this disease
that's getting a million people a year, and on the
other hand, we can't recruit a few hundred people.

From an AIDS perspective, having gone
through an inability to recruit people into AIDS
clinical trials when we had lousy agents, despite a
desperate need to incredibly easy to enroll
patients when we had very good drugs, despite the
same desperate need.

I think that one reason it's so hard to
enroll on the feasibility side is that we actually
have very good agents, and we like to talk about the sky is falling soon in terms of drug resistance. In this setting, it is not. And so I think we should listen to the fact that the reason it's so hard to recruit is that there is not a screaming need for these right now. It is improvident to assume that we will not need them, but I do think that someone should say aloud that there is not a screaming need right now. And that is as big an impact, I think, on feasibility as anything else.

DR. MOORE: Thank you. Ms. Young?

MS. YOUNG: So I, for one, will admit my head is aching, but I do applaud the FDA process that has gone forward, and very deliberatively. Industry has had many chances to have input, and I think the issues that were initially not resolved are somewhat resolved. At the same time, I'd like to encourage industry to stay in the business of antibiotics. And I realize that trials have to be set that are feasible.

I think the consumer's interest, the groups
that have spoken, are to have antibiotics that actually are not inferior passed. So I think it's very important that we objectify, as much as possible, any of the endpoints. So I would say symptoms and signs, pharmacometrics, any kind of objective information, and it should all be weighed somehow. And I would hope that we would get more innovative-type drugs, not more me-too drugs coming out of the process.

In terms of margin, I would say the non-inferiority margin should be 10 percent or less just because of the inherent biases in the non-inferiority trials. Thank you.

DR. MOORE: Thank you. Dr. Weinstein?

DR. WEINSTEIN: So I take note of Kent's pointing out the bias in the membership of the FNIH group, but I actually thought that the document that was produced was informative and well-reasoned, and I really couldn't find much fault with it. I think, at the end of the day, it represents progress. And so I am supportive of the interim recommendations for these endpoints, with
the understanding that more research is going to go forward.

I agree that the descriptive terms could be strengthened by some way, to quantify them. And I guess I would encourage looking at some way of doing this, akin to what's been done for the 10-point pain scale with numbers and with pictures of various grimaces, and that that might be helpful.

DR. MOORE: Thank you. Dr. Cappelletty?

DR. CAPPELLETTY: Yes. I'm in support of the 3 to 5 day as the primary endpoint. I think it keeps the clinical trials in line with how standard of practice currently is, given that patients do need to be discharged within usually a 5-day timeline for community-acquired pneumonia or risk losing money in the process. So that incentivizes to stay within those parameters as well.

I think it'll be interesting as the data evolves to see if we do see a change in the microbiology. We are seeing more staph aureus, more MRSA. Would that still fall within an appropriate 3- to 5-day response time, or will we
see differences in that as time goes on? And if we start enrolling patients with a greater severity of illness, again, would that 3- to 5-day timeline hold true, given that a good portion of patients really are at a PORT III level of severity when they're admitted into the hospital and enrolled into these studies?

So I think there's a lot of data that will be forthcoming from these, but I think we're at a great starting point with all of that.

As far as the margins, I'm not a statistician by any means, but what the statisticians have said today, I would be in support of, the 10 percent margin.

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

DR. D'AGOSTINO: I think the symptom measurements make a lot of sense. And my concern was, are they standardized. And from the discussion, it appears that we really are at a stage where we're at the beginning of these type of studies, where these are going to be used and standardization will need to be addressed. As so
the signs, I think the signs are important, but
maybe less so, as a secondary.

I'm still concerned about the ITT versus the
per-protocol. And I think as we go into some of
these trials, we'll see how the as-treated start
actually looking versus the full ITT population.
But what we want is a good analysis sample.

Thinking in terms of the micro-ITT versus
the full dataset, we'll talk about that in the next
question, but it to have two studies with ITT and
then once a combined dataset with micro-ITT, I
think those make a lot of sense. How we want to
put priorities on them, we'll talk about later.
But in terms of this question 1, I think that those
make sense, and I think the margins from what we
have in the historical databases make sense. It's
very loose. And as Tom mentioned, these are things
that we do in other arenas with much more rigor.
And I think that you're going to be in a
situation -- you may very well be in a situation
where things like biocreep, that the standard of
treatment may start changing, or the thing that's
called a positive treatment, and your particular trial is different. And the margin of 10 percent may start becoming an easier and easier thing to obtain. And the success rates may move up. And the odds ratio versus difference, I think those are going to be major points that you have to worry about, and to identify them now as things to look at I think is important.

DR. MOORE: Thank you. Dr. Bennett?

DR. BENNETT: The remarks that I make will assume that this is a population enriched for patients over 50, many of whom are hospitalized. And this has to do with our ability to elicit signs and symptoms in critically ill patients who may not be very conversant. And so they don't give us adequate data.

But I still think that an early time point is critical, because at that time, as Dean Follmann was pointing out, there are less non-random events occurring, where people are being lost to follow-up or having allergic reactions or other co-morbidities that interfere with finding the
endpoint.

So early time points are good. Now, what about using symptoms? I'm convinced, like the rest of you, that that's a good way to go. I'm also convinced that it's very subjective, and we could get into trouble with that. So we have a learning curve to find out, actually, how to use those symptoms.

We certainly agreed we can't use mortality. It's just too low. That's good, but it means that we would have to have huge trials to look at mortality.

Now, what about the microbiologically proven population? As I have indicated, I don't think it's all that proven, and I would definitely make it a secondary endpoint. It's absolutely important to look at, but I can't see it being valid enough to make it a primary endpoint.

About prior antibiotics, I think accepting a single dose for a short-term antibiotic is important. You can do the studies in the U.S., and I'm not sure the effect will be big enough to worry
about with a single dose of short-term antibiotics.

So the non-inferiority margin, I like 10 percent. When I think of a person who should be responding at 80 percent and the response is at 65 percent, clinically, that's an important difference to me. So statistics or not, I think 50 percent is too high. I see where Matt is going. What's the right number? Twelve and a half, 12.8, whatever? But I think 10 percent is probably worth going with.

How many trials do we need? I'm not sure we need two. I think, as Dr. Eisenstein has pointed out, there may be situations in which we can use other data and decide we don't need two. I think that should be on an ad hoc basis.

The other issue is what do we do with these new microbiological methods, and I just don't think they've reached a point where we can use them. When I was talking about viral cultures, I'm not sure what to do with those either. So I think we'll have to -- around a learning curve there with the new micro tests. Maybe we can learn how to use
them, but right at the moment, I don't think we can. Thank you.

DR. MOORE: Thank you. Dr. Masur?

DR. MASUR: I think it's gratifying to see that we've made a lot of progress over the last five or ten years. And I think it's also important to point out what Kent said, was the sky may not be falling now, but I presume that we would all agree that the sky is eventually going to fall and that we're going to have pathogens that are not as sensitive to the organism we use. So we clearly need to stay ahead of the game if that's possible in 2011.

It's also great to see -- I think we're coming to a consensus about the trial designs that Katie suggested to us. And I don't really have anything to add. The 10 percent margin seems to be reasonable. And it's always a high-risk venture not to agree with Jack, but the issue about microbiologic confirmation, again, unless there's empyema fluid that's positive or a blood culture that's positive, everything else seems to be up in
the air. So that'll be an interesting analysis, 
but whether it will be helpful is another issue.

DR. MOORE: Thank you. Dr. Wiedermann?

DR. WIEDERMANN: I'm not sure I have a lot 
to add to all the excellent comments preceding me. 
Certainly, I have difficulty separating question 1 
from question 2 because they're very much 

codependent. I guess I would have a problem having 
a margin less than 10 percent, just because, 
although we haven't seen the numbers, I think it 
would be a big price to pay in sample size. And 
15 percent sounds like a lot, but I can't get any 
more objective than that, so I would sort of favor 
the 10 percent.

I'm actually relatively okay with any of the 
three trial designs. I would probably lean towards 
option 1 if I could get some of my wishes granted, 
some of which come under discussion question 3. So 
it might be a way of getting up some -- enrolling 
fewer patients, but getting some better data that 
will help us in the future.

DR. MOORE: Thank you. Dr. Calhoun?
DR. CALHOUN: So let me add my kudos to the FDA. You folks have kept your nose to the grindstone on a very, very thorny problem. and it's clear that linear progress has, in fact, been made.

You take your share of criticism when things don't go so well, and you should take your share of credit when things do.

In terms of the endpoints, the symptoms at 3 to 5 days do appear to provide some differentiation. Cough, and sputum production, chest pain, and difficulty breathing are all part and parcel of pneumonia. There are two others that have been raised that we might think about, which would be malaise and a decreased appetite, which are pretty common as well.

As mentioned, objectifying those symptoms is the key. And, point of fact, that's not uncharted territory. There are some interesting, novel, technological approaches to cough counting that can be done with recording devices, and so you can get a metrication of cough frequency in that way.

Someone mentioned using a pain scale to get
to chest pain. There are certainly validated
dyspnea scores. Now, admittedly, those are for
chronic dyspnea and not acute dyspnea, so there may
have to be some revalidation done in that regard.
But there are scales for dyspnea out there. For
malaise, I don't know what to do to quantitate
that. Appetite, you could do calorie counts or you
could do meal counts.

With respect to objective measures, yes, I
think that -- I'm a little more sanguine about
objective measures. And we'll come back to where
they position when we talk at the next question.
But I do think that temperature and arterial oxygen
saturation, as measured by pulse oximetry, can be
done pretty reliably in a clinical trial setting
because the same instrumentation is used, and the
same methodology is used, and there's an SOP, and
those could be objective measures that could be
factored in -- I'll put my nickel on the table and
say, secondarily -- behind those four symptoms.

Vis-a-vis the non-inferiority margin, I've
already made my comment that maybe risk ratio or
proportional hazard makes a little more sense to me.

We also need to have some understanding of the stability of these symptom measures. I think John Rex mentioned, from yesterday to today, patients are probably pretty good at telling us whether they feel better, whether they feel not so good. If we're looking at an endpoint visit that's two weeks out, that might not be so good. So I think we need to be sure that our scales have some longitudinal validity, temporal validity as well.

DR. MOORE: Thank you. Dr. Shyr?

DR. SHYR: So we've heard the difference between biostatistician and the clinician a couple of times, traditional things. Let me tell you, I cannot -- or I don't remember how many times when my investigator gave me the data with non-perfect designs. And when I give them beautiful p values and go back to them and say, "Well," Dr. So-and-So, "be careful, this p value is true only if A, B, C, D, E." And then my colleague presents this beautiful p value and sometimes forget what I say,
you have to say, A, B, C, D, E.

[Laughter.]

DR. SHYR: That's why the statisticians like the rigorous design. But also, on the other hand, from late 2009 to today, we do see a big progress about endpoint. Remember that time we discussed the mortality. It was hard to find a margin.

Now, we move to symptom. If you ask me, symptom is hard enough? No. But am I willing to support it? Yes. This does not mean we do not need to continue to develop the standard, a new standardized tool to measure all this. What we want is harder. The reason we want this harder is we want the data as interpretable. When I give back the p value to all of you, the people can interpret that, right? The harder is the better. But at this time, we have to balance between feasibility, if it's feasible, or the idea. So I support the symptoms of what we propose here.

But I do want to mention one thing. The reason we pick 3 to 5 days is, we believe that is the largest difference. We cannot ignore, at least
we need to build a futility-stopping rule for those 13, 14 days, what's called at time -- the test of cure means those are long term. Does the benefit carry on or not?

So for that portion -- and now we move to the signs. I do think we should collect the signs, which is important. We heard a lot of clinicians comment. But now we don't have the evidence, again, to show the signs that biomarker is the cause of that. I think if we have the data to prove, I'm willing. Sure, we should include that in the future, but I think we should collect that data very rigorously. Okay?

About the margin, I am a statistician. I look at the data. I look at the data and determine the M1, so I 100 percent support 10 percent because that 10 percent is really based on the data, which we have. It's not ideal. Again, that's not randomized, but it's still okay.

Back to the micro-ITT, back to the ITT, yes, we know it is toward to know. Especially, this is important, which I haven't heard today mentioned,
the quality of the trials. It's important. The compliance is special, the blinding. So those kinds of things, we have to mention. Be careful when we round -- this is because it's toward to the known (indiscernible), which maybe is the problem for the non-inferiority trial, that ends up, I want to support a micro-ITT because that is the disease we're interested, period.

DR. MOORE: Thank you.

Dr. Rex, did you have anything you wanted to add?

DR. REX: Yes. A couple of things, because there were a few things that were going around the table, where I thought I might add something.

First, I want to say -- I want to echo my comment -- and everybody else's comment -- about the FNIH process. The early symptom-based endpoint is imperfect. It has flaws, but we really appreciate what it does for us. And if we don't make use of it, we remain stuck. And I said earlier, all three designs make good sense. I think industry needs flexibility.
The proposed margins, I didn't comment on, 10 percent on ITT, 15 percent on micro, proven. They make good sense. But I do want to at least briefly meditate on why we like the number 10 percent. Dr. Wiedermann asked, "Why 10 percent?"

Well, it aligns with the number of fingers and toes, and it has a nice typographical symmetry. But dogs have four toes per paw and cats have four toes per paw in the back and five in the front. And if we were of the quadro-toed family and thought in base 8, then a nice symmetrical figure of 10 percent in base 8 would become 12 and a half percent in base 10.

Is this a logical way to pick a margin? You decide. But the number 10 percent, as you say, people like it, but I want to point out just how flawed it is.

Anyway, it works for me, and the resulting clinical trial program is big enough without being too big; it's like Baby Bear's porridge. It'll usually provide an adequate safety database, which
I like. I mean, that's good. I mean, I can kind of get it all done in the para-study, so that's nice. And provided we find a reasonable pathway forward with the prior antibiotic issue, which we need to discuss next, I think we have a path.

I was also pleased to hear Dr. Laessig provide a sense of the current agency thinking on the trial population for oral drugs and make sure PORT II and PORT III -- I think that's probably feasible, and that actually is a path that's very helpful.

Dr. Neely asked about why we study agents in the non-inferiority setting to begin with, and sort of this question of do we need more antibiotics, and I really do feel obliged to comment. You've hit upon the paradox of resistance. In brief, we do want new drugs for bad bugs, but, paradoxically, we're forced to study new drugs against not so bad bugs.

Think about it. If I have a new drug for methicillin-resistant staph aureus, the one comparator I can't use is methicillin. All right?
I'm not allowed to set it up. I must study my new
drug in a study where the comparator doesn't
really -- I can't do it where the comparator
doesn't really work. I have to pick a good,
quality, active comparator, and I must exclude the
most resistant pathogens.

So this problem is actually very, very, very
subtle, and at its deepest level, it's a real
challenge for those of us who want to develop drugs
for resistant pathogens, which are not yet
widespread. And I think somebody else commented on
that.

If you want to be proactive before the
tsunami, we in industry have a real problem and we
currently need to talk closely with the agency
about indication-independent, pathogen-focused
approvals, because, otherwise, we will not have
drugs approved in advance of certain tsunamis that
are coming.

So we do the studies we can, CAT scan,
intra-ab, and UTI. If you want new drugs, these
are the only possible paths to registration, and we
need to support use of these paths. It's worth saying again, we cannot make companies work in this field. We must make them want to work in this field. And infeasible designs are a great way to cause people to run, fleeing for the hills. I want new antibiotics. This is a good tool, so I'm in favor of what's happened here.

DR. MOORE: Thank you. Okay.

We're going to take a break here in a second, but let me throw this out to the committee. Most of the discussion we've had regarding the first question has followed along -- has also involved discussion of the second question.

So what I would propose we do is go around the table one more time, specifically addressing any unanswered, unstated opinions about question 2, then we'll take a break, and come back, and consider each of the elements of question 3, which I think are going to require a little bit more amplification and discussion.

Dr. Cox, did you want to -- can I get you to reread question 2? And then we'll go around the
room.

DR. COX: So question 2, please discuss the merits and limitations of each of the proposed development pathways in trial designs, and that's referring to options 1 through 3. In your discussion, please comment on the use of improvement or stabilization of clinical signs of pneumonia as a co-primary endpoint versus its use as a secondary endpoint.

DR. MOORE: So there, again, most of the discussion has already been made, but I just want to make sure everybody gets on the record before we move onto the third question.

We'll start with you again, Dr. Reller. Any specific comments you have not yet made about this?

DR. RELLER: Actually, the first go-around, I answered question 2 and not 1, so I'll answer question 1 now.

[Laughter.]

DR. MOORE: Sounds great.

DR. RELLER: Ten percent non-inferiority margin. But applied to question 2, I mean, I'd be
willing -- I mean, if I had -- 1 or 2 I think would work. Either one would work. I am reluctant to totally -- I mean, one could argue about which signs to include, but I think some resolution of objective findings in addition to the symptoms is important.

DR. MOORE: Thank you. Dr. Roberts?

DR. ROBERTS: I would echo that. I have a question for Dr. Laessig.

On the "at least two abnormal vital signs" part of the study population, there's some of PORT and there's some of CURB-65 in there. And how exactly did we come up with these parameters, specifically? I don't disagree with them. I'm just interested to know.

DR. LAESSIG: Well, we had a lot of discussion. Some of them I think were based also from --

DR. NAMBIAR: Attainment of clinical stability.

DR. MOORE: I'm sorry. I missed that last point.
DR. NAMBIAR: Clinical stability.

DR. MOORE: Thank you.

DR. ROBERTS: Yes. Because as a pulmonary critical care guy, I'm looking -- if I see two of these, I'm probably going to be approving a unit bed, specifically hypothermia or hypotension. And you may have covered this already, and I apologize. But does this exclude milder forms or milder manifestations of community-acquired pneumonia?

DR. LAESSIG: As we've currently written the draft guidance, those were the abnormalities we were looking for.

DR. MOORE: Thank you. Dr. Fleming?

DR. FLEMING: So coming back to the context for the 10 percent margin, which I think many have supported, I have supported, my sense is, the way forward here, we're looking at trial designs that are in the 1350 to 1950 range. I endorse the proposal that this could be a single trial, then supported by other data, as has been laid out by the FDA. So, therefore, we're looking at that size as the entire development plan.
I would agree with the proposal that the non-inferiority assessment for micro-ITT would be the primary analysis, but we surely would give attention to the supportive analyses, the overall ITT assessment, as well as signs. Assessments of signs would be key secondary.

What's driving that sample size under that paradigm is the fraction of people that you get in as micro, that's confirmed micro, and were assumed to be 27 percent. We'll discuss in question 3 creative approaches to try to enhance our sensitivity, enhance that. If we can get that fraction up to 40 percent, this sample size drops to 1300, as the totality of the evidence that we would need from the single trial to get registrational approval.

So, in essence, a single trial is okay, the NI margin of 10 percent on the micro-ITT with attention given to supportive analyses for the overall ITT, for signs, also focusing on ruling out bad things happening at day 21, and hoping to try to enrich the micro-ITT as much as we can, since
that could bring down the total sample size.

DR. MOORE: Thank you. Dr. Fratzke?

DR. FRATZKE: Thank you. All I want to say is I do also support the 10 percent margin.

DR. MOORE: That's fine. Thank you. Dr. Goetz?

DR. GOETZ: I certainly accept the 10 percent margin. Going through the three trial designs, I do echo the thoughts of others that all three of them seem to be acceptable to me. I don't have a strong opinion on that. I think that everything we do amplify the number of patients who have a microbiological diagnosis will serve us very well.

I think that in the current trial design, it's going to be very important, particularly as we're looking at subjective measures, to make sure that everyone is blinded to the arm of the study, the patient is armed, because there are clear issues with the potential introduction of bias as a consequence.

Let's see now. My other points have been
made by others, but the early endpoint I think really serves us well because in terms of which population to look at, the per-protocol microbiologically proven modified intention-to-treat population, if I got that all straight, is the important one. And by looking at an earlier time point, we really should lose fewer patients to protocol violations, and there would be greater fidelity of the study results as a consequence and concordance between the different populations.

Not discussed here, I think implicit in these study designs is not only to look for successes, but look for failures so that people who, during the first three days of study, progress to requiring mechanical ventilation, pressure support, hemodialysis, or other life-supporting measures, while they may not be microbiological failures as such, we certainly want to be looking at them as treatment failures. And I think I'll stop there.

DR. MOORE: Thank you. Dr. Neely?

DR. NEELY: I think they're all good. My
order of preference is 3 first, because one less
IRB submission, one less set of site monitor visits
and binders is as good thing. And I think that the
money, as I said before, is going to be in the
hospital-acquired if we’re looking at testing for
antibiotics for resistant bacteria, so
extrapolating to a community-acquired setting is a
good thing. One, I like next, number 1, because it
has a smaller sample size.

DR. MOORE: Thank you. Dr. Follmann?

DR. FOLLMAN: Of the three options, I
really preferred option 3 to 1 and 2. And as I was
reading this, I just thought about it. Simply I
thought, mITT is really what matters, and let's
look at 1 and 2. They have a 15 percent margin,
and so I'm wedded to the 10 percent margin, so I
didn't like it on first principles.

Also, if you think about option 1, you could
win on the 15 percent margin, if you're playing
that game. And then you're also obliged to win on
the ITT margin for those two so-called separate
studies. And what point does that serve? To me,
it seems like you're flipping a pointless coin.
And you drop your power from 95 percent, which is
what you have, if you have a 15 percent margin for
option 1, to 80 percent. So it seemed like you
were going through additional hoops, and that for
me, mITT is really what matters.

Option 2, I felt there was this additional
pointless hoop to go through to have a margin for
the signs. And so that's why I really preferred
option 3, because I believe in the mITT. It's
important to study the people that have the disease
that you have. And later, as others have talked
about, we'll discuss how to maybe enrich that so we
don't have such a burden with sample size.

Option 3, though, is really one big trial.
And usually we don't like one big trial for many
reasons. We like the idea of reproducibility in
that it's not a fluke occurrence and so on. And so
it's with some hesitation, I still endorse
option 3. And I think it's important to have -- as
mentioned in option 3, other evidence of
consistency, maybe in another indication, maybe
looking at the treatment effect by the MIC or the AUC-MIC ratio, which is kind of like a pharmacokinetic kind of perspective on it. But these additional things I think are what would make me sort of okay with option 3, as my preferred thing, as one big trial.

Yes. That's all I have to say.

DR. MOORE: Thank you. This is Dr. Moore. I like option 3 because of its scientific rigor, but the reality is that it's infeasible, in my opinion, based on the current status of microbiologic testing and the need for enrollment of a large number of patients, as was mentioned earlier, in order to get microbiologic information.

As a result, I think, just by default, either option 1 or 2 are fine. As I said before, I think that inclusion of the objective data is critical. Whether it's a co-primary endpoint or a secondary endpoint is a statistician's dilemma that I'll defer to them. But as long as firm objective data can be included with either design, I'm fine with that.
Dr. Sepkowitz?

DR. SEPKOWITZ: Number 1 and 3 are fine with me. I would still caution against the co-primary endpoint of more data points, and a larger aggregate endpoint usually sounds very logical at the time and totally backfires.

The issue of how big does it have to be to have a micro endpoint is for the discussion, I guess, after our break. But I actually am more optimistic that we could squeeze more than 27 percent out of the population, and, therefore, number 3 would be the most attractive.

DR. MOORE: Thank you. Ms. Young?

MS. YOUNG: I'm not sure if you have an option of going to number 4 or something, but as you're considering these, I think the mITT is what matters. I would like to include some weight of signs in addition to the symptoms. The 10 percent is something that seems to make sense. There's some consensus on that one.

DR. MOORE: Thank you. Dr. Weinstein?

DR. WEINSTEIN: We're all over the lot here
because, if I were voting, I'd vote for number 2 first, number 1 second, and number 3 third. And I'll save my negative comments about enhancing the micro-ITT.

That's right. I am the microbiologist.

[Laughter.]

DR. SEPKOWITZ: That's very disheartening.

DR. WEINSTEIN: I'm sorry, but I'll tell you more later.

DR. MOORE: Thank you. Dr. Cappelletty?

DR. CAPPELLETTY: I think I'm pretty much in line with everybody else here. I do like the single trial with the micro endpoint as being the important. I do share concerns with our ability to increase the micro yield to make the sample size reasonable, and from there, option 1 is my second-line option.

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

DR. D'AGOSTINO: I would just do the reverse. I think option 1 is probably the easiest, in terms of if you have two trials, operational, you look at the ITT, but then you combine them to
the micro.

    Option 3 would be the second.  Option 3 reminds me -- I'm sorry for taking a little time in this, but option 3 reminds me, when I was a young statistician, somebody came to me and said that they ran a big trial, and they had success on it, and so forth.  They said, "But damn it, the FDA wants two trials.  Should I split the one I have into two trials?"

    This is going to be my multi-center, multinational, and so forth, so it's probably going to be like two trials, and how you put the IRB petition together is a different matter.

    Because of the discussion about the vital signs and what have you, I think putting it as a co-primary isn't a problem, so I put option 2 aside.

    DR. MOORE:  Thank you.  Dr. Bennett?

    DR. BENNETT:  I have some concern that, after the excellent work by the FDA and the hard deliberations by committees like this, we're still going to not be able to enroll patients because of
the problem of getting sick patients enrolled in a study in the U.S. So the sicker they are, the less they want to read those 20 pages of informed consent. Then you try to find out who's got the durable power of attorney, and the family wants Uncle Gus admitted to the hospital, not worrying about some form.

So we end up studying patients who are of less interest. And I don't know how to solve that, but it's a bigger problem in the U.S. than it is overseas, and it's one of the things that's driving these studies overseas, and I don't know how to solve that.

DR. MOORE: Thank you. Dr. Masur?

DR. MASUR: I'm glad we're all coming to consensus on what we can control.

[Laughter.]

DR. MASUR: I'm always haunted by the decisions we make on the basis of one trial, where the one trial turned out to be misleading, but it would certainly be desirable, if we're going to do one trial, that was done in the United States and
It would be nice if, as Jack and Barth say, we could change the practice of clinical research in this country with this initiative. And if we can do that, I think somebody here should get a Lasker or Nobel prize, and maybe that's what we should shoot for.

DR. MOORE: Amen to that.

Dr. Wiedermann?

DR. WIEDERMANN: I don't think I've changed from my earlier vote for option 1, although Dr. Follmann's comments on the pointless coin toss I think are pertinent, something to consider. And I thought I was going to ask a really stupid question, but now I don't feel so bad, based on Dr. D'Agostino's comments.

[Laughter.]

DR. WIEDERMANN: Two studies versus one study, I don't care. And some of the studies we've discussed here today, they're two studies, but
they're not that different. And I'm not aware of anything in proposed guidance that says how different studies have to be, to be classified as two. So if there isn't anything like that, maybe we shouldn't dwell on that too much.

DR. MOORE: Thank you. Dr. Calhoun?

DR. CALHOUN: So my vote for 3 versus 1 as being on top really turns on how the agency plans to do the primary analysis. If you folks are going to require the micro-ITT as the primary analysis, then I'm kind of compelled by Dr. Follmann's comments, and I'd put option number 3 at the top. If you're not going to use that sort of analysis, I'd probably, for a couple of reasons, put option number 1 at the top.

In either case, I've been compelled by the biostat folks that co-primary endpoints in option number 2 are a decided second choice.

DR. MOORE: Thank you. Dr. Shyr?

DR. SHYR: Yes. I think design 2, basically, everybody agrees looks at least favored. I also agree. We pay the price to get the sample
size very high, but we get due endpoints, but, unfortunately, I don't think we have strong evidence right now that vital signs is strongly directly related to the outcome. So I will put that as my last one.

For 1 versus 3, I will pick 3 as better than 1. Again, 3, you have the micro-ITT and the plus 10 percent margin. And as I say, you round non-inferiority trials in practice is very challenging, but you have one great team to round this high quality around the 1 -- so 1 is acceptable, but if you really have to ask me to vote, I will say 3, 1, and 2.

DR. MOORE: Thank you. Dr. Rex?

DR. REX: Option 3 contains a trap. If we're saying that the only valid trial is one that uses a 10 percent margin over a micro-proven endpoint, then option 3 might be okay. But there's a proviso, but the might is very deliberately chosen by my voice. It's a large trial program for a single indication. The real trap is that option number 3 presumes that another trial is possible in
another indication. Notice the proviso, successful HAP or successful skin.

There might be other options, but the presumption is that another trial and another indication. because, to date, we are not permitted to use a single clinical trial with confirmatory evidence approach. The Carl Peck 2002-2003 workshop approach has not been accepted for anti-bacterial agents. So I'm expecting to have to provide a second clinical trial.

What if the drug doesn't do those things? What if all it does is CAP? Am I now forced to do another CAP study to get my traditional second study? That's nice.

Now, if you can deal with 12 and a half percent, base 10, which I'll remind you is 10 percent, base 8, then I can certainly go with option number 3, and I could go with 2 of the trials, maybe, if that's what I had to do, if that was my only way forward. Because if it was my only way forward to purely a CAP drug, I still have to get an adequate safety database. Maybe I want
those 2,000 patients. I'd have to play with it a
little bit.

But, otherwise, option 3's a trap that puts
us right back where we started from, an infeasible
design that blocks development.

DR. MOORE: Thank you.

Okay. Let's take a break. We're going to
now take a short 10-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'll resume at 4:10. That's what time
I have. Right? Yes. 4:10. Thank you.

(Whereupon, a recess was taken.)

DR. MOORE: All right, ladies and gentlemen,
it's past 4:10. We really need to get going in
order to finish on time or at least close to time.
So I'll ask everybody to take their seats, end your
discussions at the back of the room, please, and
come on down.

So as we go onto the discussion of the third
question -- I know we're missing some people, but I
think we should get started just the same, in the
interest of time -- Dr. Cox, would you do me the
honor of reading the third question, please?

DR. COX: Right. So just to get everybody
back on the same page, for question 3, we're
looking for advice from the advisory committee on
four topics. The first one has to do with issues
of receipt of prior anti-bacterial therapy, so
things might come up there, include excluding
patients with prior anti-bacterial therapy and the
discussion about it. Is there some allowance for
shorter courses of therapy, certain agents, or
other ways to approach the issue?

Number B, talking about methods to enrich
the micro-ITT population or the ways to get more
patients who have a microbiologic diagnosis from
those that are in the trial.

Next is C, mechanisms to overcome barriers
to trial conduct; are there certain things you can
do to facilitate enrollment of patients into
clinical trials? And then any advice on performing
clinical trials of oral anti-bacterial drugs and
ideas about approaching that and possible designs
to study an oral anti-bacterial drug.

    DR. MOORE: Thank you.

    Okay. So why don't we start again with
Dr. Reller and move around the table again, if
that's all right.

    Barth, I kept you on the hot seat.

    DR. SEPKOWITZ: All four of these at once?

    DR. MOORE: Yes. I think we'll tackle each
of them; that is, answer all four, and then we'll
go to the next person, if that's all right.

    DR. RELLER: For efficiency, I'll address
each one of those. Balance. I'm willing to give
on this trial design, but I have heard enough
negative things about prior antibiotic therapy, it
seems to me the emphasis should be on capturing the
opportunity with the new view of CMS as a quality
marker in January and seek to diminish the
sometimes inappropriate, for monetary reasons,
excessive willingness to start anti-bacterial
therapy that is comprehensive.

    So I think no antibiotic before enrollment.
I'd be willing to give on some other items in order to achieve that.

Methods for enrichment. We've heard a lot of things proposed, but, realistically, the biggest impediment to recovery of a live organism, at least from blood cultures -- and I realize this is a minority of the ways, but is the most robust way to confirm pneumonia -- in multiple older studies of the foremost pathogens, streptococcus pneumonia, is the receipt of antimicrobial therapy before the blood culture is obtained.

So I think that why I'm so keen about the first one is because I think it's the single best thing you can do to enrich a microbiological diagnosis.

Urinary antigen for the pneumococcus, at least in adults, is a good test. It's complementary to the blood culture. The sensitivity in round figures in the largest trial done, one we were involved with, is about 80 percent of people with a positive blood culture have a positive urinary antigen. But there are
also additional ones that one get that don't have a
positive blood culture, meaning more have a
positive urinary antigen. And I think it has to do
with the timing of things. It is not a way to
assess late therapy, because if it's persistent,
for weeks and weeks, out to months.

So it takes a while to be present, a few
days, but then, once it's there, it doesn't go away
fast. So I think that should be done as part of
routine enrollment. And it is, I think, an
objective measure for etiologic diagnosis. And, of
course, the antibiotics affect all of the pathogens
that could be cultivated or grown.

Mechanisms to overcome barriers to trial
conduct, I think a major issue is the cumbersome of
the IRB informed consent process that is clouded by
the imposition, as if it were a regulatory -- some
of the HIPAA requirements are not, as I understand,
and from the position paper of IDSA, because of
statutory regulations, but rather, local
interpretation of what the regulations are. And
this is a huge problem.
I think if we -- we're not talking about putting in a cardiac assist device or artificial organs. I mean, we're talking about giving an antimicrobial for community-acquired pneumonia. And why it should require a 20-page consent form is incomprehensible to me. And I think that is a major barrier. It gets into the time issue, about how much time it takes, and willingness, and what people are paid to do. And it is a major impediment, I think. And Dr. Bennett may comment on this. There was I think some internal work done even at the NIH about barriers to clinical investigation, related to consent.

So advice on performing clinical trials, I think most of the oral use is going to be in transitional therapy. I mean, I don't have anything useful to add on that, so I'll stop.

DR. MOORE: Thank you very much.

Dr. Roberts?

DR. ROBERTS: Speaking from the perspective of the mostly end-patient critical care clinician, virtually all of our patients come to us on
antibiotics, and none of them come to us with a single dose of a short-acting antibiotic. And I guess if the research is to be meaningful to us, it is in some way going to need to be inclusive. And if it's not inclusive, I guess, how are we going to enroll the patients? So I would endorse some provision made as spelled out for prior antibiotic therapy.

That said, I guess I would question along the lines of Dr. Bennett. Prior antibiotic therapy, is that really going to significantly change, in a meaningful way, the ITT population or micro-ITT population?

In terms of mechanisms to overcome barriers to the trial conduct, I would agree, the more you streamline the consent, the easier it's going to get, for whatever reason, be it HIPAA or any other constraints.

On the fourth, I'm going to pass.

DR. MOORE: Okay. Thanks. Dr. Fleming?

DR. FLEMING: I think the progress that's been made that's been very significant is that we
can now move beyond saying that mortality is the
only endpoint we can use in this setting with an NI
margin. We can use an NI margin here for the
proposed endpoint that we've been discussing;
that's the symptom-based endpoint, but under
certain conditions, under the condition that we are
looking over the time where there's clear evidence
of benefit, 3 to 5 days rather than over a longer
term, under the condition that we are, in fact,
treating people that are sensitive to and have
benefitted by the active comparator, so excluding
viral infections, basically focusing on the micro-
ITT.

Also, by evidence that I'm seeing, also we
need to be very careful about the enrollment of
patients that have had prior effective anti-
bacterial treatment, and there's now considerable
emerging evidence about this. We've heard it all.
I won't go into detail on it. But we know that
with ceftaroline, with its superiority, that was
masked by the single prior short-acting agent. And
even more importantly, I would argue, the
inferiority of daptomycin was masked by that single prior dose.

This isn't the first evidence that we have that a single dose of a short-acting agent can be effective. We can go back to the 1940s with sulfam. And Hesselman, and Volmer report evidence that those short-acting agents with single doses made a difference, and Gleason's reanalysis in 1999 reinforces this.

So this isn't news to us. This is why we know we need to treat soon. It does matter when we're giving antibiotics in pneumonia, and it does matter that we're treating soon. But, unfortunately, the flip side to that is, but then we can't ignore the effect. We can't ignore the effect that what we know matters is going to happen. And that is it's going to actually impact.

What we need, then, is evidence to show that combination therapy, when you use your active control, added to that single dose, that that is superior to the single dose. And the meta-analyses that we've had on this to look into this issue
haven't established superiority. Hence, there's no margin, i.e. --

The bottom line -- unfortunately, I wish I could argue otherwise -- is, the evidence is suggesting that once you've had that single dose, even if it's a short-acting, what you're adding to it in the active comparator, while important in the absence of that single dose, is much less important in the presence of that single dose. Hence, it invalidates the integrity and interpretability of non-inferiority.

This issue is not about the perfect. None of us think we're at the perfect. What we're striving to achieve, though, is a trial design that satisfies the congressional mandate of substantial evidence of efficacy. And you do not get substantial evidence of efficacy from a non-inferiority trial unless you can validate the non-inferiority margin you're using against the active comparator.

We can do it here, but to do it, we have to have the right time frame, we have to have the
micro-ITT, and we have to be able to ensure that we're not giving an effective prior dose that would nullify the added benefit of the active comparator.

I'm going to be very brief on these other areas. And, in fact, I'd like to hear more from my colleagues on B, C, and D. But real quickly, on B, I was impressed the way the FDA laid out the approach, at least for us to discuss, that we're going to look at conventional sputum culture, but we will try to go beyond that to do the best we can to enrich this population, to get above the 27 percent.

I like the way they said it, was in patients with high suspicion of community-acquired bacterial pneumonia, that we're going to consider some of these other approaches like urinary antigen testing, et cetera. And I'm really intrigued by Dr. Reller's insight as well, that, in fact, if we are able to prevent exposing to that first prior dose, that also might allow us to enrich.

So I'm impressed by the thoughtful way this has been laid out and am hopeful -- even though I'm
very interested in Dr. Weinstein's comments that he's going to put forward. I'm hopeful that there are ways that we can try to enrich this as best possible.

I agree with what's already been said in terms of the barriers that Dr. Temple had raised earlier, streamlining the informed consent. I'll defer any other comments. I'd like to hear what others have to say about B, C, and D as well.

DR. MOORE: Certainly. Thank you, Dr. Fleming. Dr. Fratzke?

DR. FRATZKE: I reiterate. Let's see, on the prior anti-bacterial therapy, if it's certainly going to screw up the end result of our testing, I wouldn't be for that. However, if there was any way, or maybe the first antibiotic did not affect the organism that we're after, then we may be able to use that, or some way that we could overlook some of the pre-antibody therapy.

Also, the other thing I'd like to emphasize, I really hope that we push the testing we're talking about, I think the ability to recognize the
organisms rapidly, as one person today talked about this procalcitonin technique. A thing like that would really help, I think, and so not having to just throw out an antibiotic, and start someone on something, and can get them going much faster.

The other thing, the mechanism of the barrier; not only the signed consent form being made easier, but I think also maybe the way this is introduced to the patient that comes in. Perhaps, they're going into an emergency room, was very busy and probably does not really encourage -- I think a lot of patients, I think, would really be encouraged by being part of a study if it was presented to them correctly or right. So I would like to see that; maybe we could work on that.

DR. MOORE: Thank you. Dr. Goetz?

DR. GOETZ: In order, in terms of the issues of receipt of prior anti-bacterial therapy, I fully agree that the ideal perfect study has patients not receiving any antibiotic, not even a single dose of a short-acting therapy. However, I'm also very concerned about the performance of studies in the
United States versus internationally. And if we wind up with all studies looking like the most recent ceftaroline study, wherein 96 percent of patients are enrolled internationally, I'm quite concerned about the generalizability of those studies to patients seen in the United States.

I also hearken back to the fact that clinical trials were able to demonstrate the not non-inferiority, or inferiority of daptomycin in those studies that were done, and that in ceftaroline, we do have inferences about possible superiority.

Now, that occurred only because a substantial number of patients received no prior antibiotic therapy, very clearly. So any study has to push very hard on having a large fraction, if not the majority of patients, having no antibiotic therapy. And recognizing what has happened to clinical practice in the United States, I think that does mean that a substantial number of patients will be enrolled internationally. But as long as a substantial number are enrolled in the
United States, I think that we may be able to obtain all of our goals, imperfectly, but very, very good, I trust.

Having said that, it is incumbent upon any study to ensure that microbiological samples are obtained before any dose of antibiotic is given. And, quite frankly, that means that person who popped a dose of amox clav out of his medicine cabinet before going into the ED is clearly not eligible for study enrollment. I think those are my comments about prior antibiotic use.

In terms of methods to enrich the microbiological intention-to-treat analysis, I think this goes to the severity of disease, and those people having more severe disease being more likely to have infection by a typical microorganism, pneumococcus or something of that sort, rather than a viral infection. And there are a number of tools that have been used in terms of severity. There's the CURB-65. There's the PSI scores. There's age over 50. There are the IDSA criteria for ICU admission. There's use of ICUs.
Which of those is ideal is not for me to say now, but I think there are tools available. I think that procalcitonin is another valuable tool for enriching a population, where at least one has a greater confidence that that person truly needs antimicrobials. I'm not sure how much it adds to the other aspects of severity in disease that I've discussed, but it's relatively simple -- emphasis on the words "relatively simple" -- tool that can be used. Certainly, pneumococcal urinary antigen. And if agents are being tested that are predicted to have activity against Legionella, the Legionella urinary antigen becomes a useful tool in that regard.

I guess there's a concern always about using investigational techniques, but recognizing that science moves forward, that sputum can be collected, and perhaps we can utilize a quantitative PCR at some point along the line, on sputum as well as on blood, perhaps, quantitative on blood.
In terms of issue letter C, streamlining consent, everyone has touched on that. That is absolutely critical. I think that there are other aspects here as well. In my clinical trials experience, it's one thing to present a study to a patient saying, we're looking at superiority. This drug may or may not be superior. In terms of eliciting interest in the patient and enrollment in the study, it is frankly more challenging when we're doing non-inferiority studies. Well, we don't know whether this drug is better or worse. It might be the same. It is a different kind of engagement we get from patients.

I think that emphasis needs to be given as to how we -- you cannot provide incentives as such for people to enroll in studies, but we have to provide them with cogent reasons as to why they should participate in studies and why it's maybe not to their benefit, but to society's benefit for them to participate. And then there are structural aspects. The NIAID approach of putting a tremendous number of resources into a few sites is
useful. And I think there are other strategies of supporting multi -- basically, networks of emergency rooms, because, frankly, these patients are going to be enrolled primarily out of emergency departments unless we partner with our ED colleagues. I'm not the person who's sitting in the ED all the time myself.

In regards to oral antimicrobials, clearly a transition from IV to oral makes good sense. We have to look at the duration of therapy here. In terms of all oral therapies, we're looking at a lesser severity of disease because those patients will be hospitalized. I'm thinking that procalcitonin may also be useful in that regard.

DR. MOORE: Thank you. Dr. Neely?

DR. NEELY: Regarding point A, I don't need to repeat. I think Dr. Goetz basically made most of the points that I would make. I recognize that the perfection is to have no prior antibiotics, and maybe the wishy-washy response is to say we could strongly discourage prior antibiotics in every way possible, but not completely exclude it.
In terms of enriching the micro-ITT population, I'm not a statistician, but I wonder if we could take maybe a grated or an interim approach as we're learning more about these methods, so that we have different sample sizes, based on different rates of positivity, assumed rates of positivity, and we could do interim analyses along the way, and say, "Look, at this point in the trial, we actually have a 40 percent isolation of organisms using these combined approaches, and, therefore, we can maybe stop the trial earlier because we have a smaller sample size." I'll leave that to the statisticians to consider.

In terms of overcoming barriers to trial conduct, I wonder if, with the mandate to go electronic in all healthcare settings, whether we'll be able to implement some flags. For example, if somebody registers in the emergency room, if they are registered with the chief complaint of shortness of breath or something that would suggest pneumonia, that immediately a flag would pop up that they may be eligible for this
study, and the mechanism to get them enrolled would happen that much sooner.

I agree with what Dr. Goetz said, too, about the difficulty of selling a study like this to a patient. And it gets back to my earlier comment about, is there really a burning need for new antibiotics today in community-acquired pneumonia? And I would argue, with the exception of MRSA, that's a questionable need. I think there's a future need, as we've discussed.

So, again, I think we need to encourage the drug companies to provide drugs that have some other benefit associated with them that we can use to sell to patients, at least, certainly in Los Angeles, it can be difficult to enroll minority populations in these studies, in any clinical study.

Then I do also echo the concerns about the paperwork burden associated with the huge informed consents. And I wonder -- I don't know who the people are to talk to, to try to make this different, but maybe we could have a step-wise
approach, where there's a kind of mini-informed consent that's one page long, that gets done for the first dose, and then they have time to review a longer consent document for continued enrollment, or emphasize that they always have the option to withdraw.

We do this in pediatrics. We have a one-page assent document for young children. And it has very simple language, and it can't be, really, more than a page long. And they have to give their assent in addition to the parental consent to be enrolled, say, for any child over the age of seven. So maybe we adopt an approach like that to speed up enrollment.

I think my only comment on D for oral is that perhaps there could be -- if there's no IV formulation available, then to me it would seem that we're talking about outpatient setting altogether. So, certainly, the American Academy of Pediatrics has made a big push for practice-based research networks, community physicians banding together to do clinical research. And maybe that's
a forum or a setting that studies for oral antibiotics could be done.

DR. MOORE: Thank you. Dr. Follmann?

DR. FOLLmann: Just to start off, to amplify on a point Michael just made, he was talking about adaptive designs. And if we consider option C, I guess, or 3, which was to focus on the micro-ITT population, the trial says we should enroll about 1860 patients. A better way to do that is probably just to wait until you've enrolled 500 who are mITT-positive and then you can stop. So it's just a better way to conduct the trial, kind of like waiting until you have a certain number of events in a mortality trial, say, as opposed to randomized in a certain number of people.

Getting back to the letters here, I don't have much additional to say about the receipt of prior anti-bacterial therapy. I thought the evidence was strong in that it can't be ignored and that the arguments to allow it are basically practicality arguments, which, to my mind, aren't as strong as the argument about it contaminating
the ability of this non-inferiority instrument, which is, in my mind, weak to being with. It's something that I wouldn't favor here.

Methods to enrich the micro-ITT population, I don't have much to add to that about what's been said, except I think our goal here is not really to make a definitive diagnosis for a specific patient. It's really just to broadly enrich it. And so I think it's reasonable to have less accuracy for these methods to enrich the population than we would require for licensure to get a definite result for an individual patient. So I think you can be a lot looser with that.

There is maybe a potential concern, though, that with these new methods, you might be able to identify organisms which aren't really the cause. I can't say much beyond that. It's just maybe a potential concern.

Just to talk about a couple other general design issues, I think I mentioned earlier the non-inferiority margin of 10 percent is really wedded I think to an 80 percent success rate. If it
deviates from that, things are in jeopardy. And so
I think it's more natural to have like an odds
ratio or some kind of moving margin that calibrates
to the overall event rate.

Then I was sort of heartened by the NIH CAP
trial, where they're hoping to get consent within
an hour. It seems like if you could do that, you
could probably wait until then to give them the
antibiotic that's involved in the study. So maybe,
if the NIH is successful with that study, it'll be
encouraging for this field as well.

DR. MOORE: Thanks, Dean.

This is Dr. Moore. So it seems to me that
no community-acquired bacterial pneumonia trial
guideline will be perfect, but I believe it's
possible to find and enlarge the sweet spot of
convergence in the Venn diagram, where a clinical
trial can be ethical, scientifically sound, and
financial feasible.

Obviously, I think we could all agree that
the current limitations on the performance of
clinical trials in the United States have led to
most clinical trials being performed overseas. And I think the pendulum has swung, rightly so, towards better protection of patients, but that's unfortunately come with an onerous, I think, apparatus at the IRB level towards administrative and bureaucratic barriers, supporting efforts in preventing efficient conduction of clinical trials in the United States.

So as Dr. Bartlett pointed out, the microbiologic milieu is different outside the United States. And a case in point that leads to some caution in interpretation is that when the ceftaroline -- last year at this time, the ceftaroline committee was convened to consider ceftaroline. And the majority -- that is the largest group -- of patients enrolled in the focus group were actually enrolled from Romania, which has been shown to have a significantly different microbiologic milieu from the United States. And, frankly, it makes it difficult, I think, to make accurate inferences on the drug's performance in U.S. citizens.
So having said that, the biggest problem we can discuss -- we have discussed prior antibiotic therapy and other mechanisms to overcome barriers to trial conduct, but I think the biggest barrier is going to be somehow reducing the regulatory and administrative barriers to conducting clinical trials, yet, at the same time, protecting patient safety and patient health.

So as was mentioned before, shortening the informed consent and making the trial conduct easier, those are the things that are easily said but are the biggest hurdles to overcome.

Having said that, I support allowing the enrollment of patients who have received a short-acting antibiotic from the data that have been presented earlier today. What remains to be seen is what Dr. Reller had alluded to, which is the effect of the change of the CMS guideline, the six-hour antibiotic rule on enrollment. It remains to be seen whether that alone will allow for a greater number of patients who will not have had an antibiotic prior to enrollment.
Ways to enrich the micro-ITT population, I think if tests like procalcitonin can be developed and hold their promise, then I think that population could be enriched, but that remains, right now, an unrealized goal. Similarly, use of point-of-care tests are ideal, particularly if you have a hospital set-up that's different from Johns Hopkins; I mean, that is if you have -- if you don't have an in-hospital lab, or, more specifically, earnest young medical students with a sense of urgency who will make that half-mile stroll to the lab with that specimen, then you may have difficulty in getting your micro-ITT population enriched.

With regard to overcoming barriers, specifically the trial conduct, we discussed rapidly enrolling patients with CABP, as we do with patients with MI and strokes. There, again, I think it's a lofty goal, but one which is going to require a change in thinking that has not been present for quite some time among physicians and ER staff. The example is that certainly patients with
sepsis are enrolled quickly in clinical trials, that is triaged more quickly than patients who are not. And that really -- perhaps if it were phrased as sepsis due to pneumonia or sepsis from a pulmonary source, perhaps that would be a way to overcome that.

Lastly, I'll say about performing clinical trials of oral antibiotics, the insistence on an IV formulation for a patient I think will lead to the exclusion of most U.S. patients for a variety of reasons because, number one, it's not the way we practice. Patients are going to be reluctant and insurers will be reluctant to pay for prolonged hospitalization simply to address an issue with IV formulation. Even if patients go home with a PICC and receive IV formulation of an experimental drug, that also has risks of its own with increased rates of DBT, and PE, and use of Coumadin as a result, in addition to other problems, such as infected lines. I think it would be most reasonable to allow a switch to an oral antibiotic to remove that barrier.
That's about all I have to say for now.

Dr. Sepkowitz?

DR. SEPKOWITZ: So it seems like A and C are very closely related. I think we need to have better information, and Dr. Shlaes mentioned that, in a trial he's associated with, 860 people were screened; 220 had had previous antibiotics. That can be looked at as half full or half empty. To me, that shows that prior antibiotics are not the majority problem here; there are many other problems.

On the other hand, it would be really useful in his data and in Dr. File's data to distinguish antibiotics that were given in the ER as part of an ER protocol, as first dose, versus the person who pops the amoxicillin from the cabinet. That's knowable data, and there's a huge difference.

If the majority of the pre-antibiotics are people who, because of ER protocols, are getting a hit, then that's very fixable. If it's people who grab the medicine cabinet, pop a pill, and come in, that's a very different set of problems, but I do
think that's knowable.

We have a mish-mosh where we have two different causes of previous antibiotics that are totally different in terms of why they happen, and I think we should work to distinguish the two.

We've sort of taken the high road that the real problem is regulatory and big government, and we're becoming tea party people or something like that.

[Laughter.]

DR. SEPKOWITZ: I think that there's a huge disincentive in the U.S. for trials of me-too types of agent, cefta this versus cefta that, at the selfish, selfish investigator level. There ain't much money in it. There's no papers in it. You're always discouraged, in a career sense, to do it.

I think the flip side is in Romania, a thousand bucks, which gets eaten by my hospital -- I would never see it. A thousand bucks to a Romanian practitioner is an enormous amount. In addition, the provision of a free antibiotic to a Romanian patient is enormous.
So it's not just the differences in regulatory burden at all. I think that's quite naive. And I don't think it's the ease with which -- or the proportions with which -- the proportions of people who get earlier antibiotics. It's much more complicated than that, and I think we're taking a really facile approach to blaming this one thing, which is we can't do it because they're all on antibiotics. They aren't all on antibiotics. Dr. Shlaes showed us they're not all on antibiotics. That said, they must not be on prior antibiotics or it's a useless study would be my view.

Methods to enrich the micro-ITT population, being a big believer in everything that ever is written in CID, I do think the Johansson study from last year is very exciting.

Mel does not, and we're going to hear from you.

But they did pick up 18 -- 180 people; 18 of them were diagnosed by PCR only for either pneumococcus or mycoplasma. That would be a big
enrichment. That would make this life a whole lot easier.

I think, finally, I can't believe that this group is falling for procalcitonin. It's just a sed rate. I can't believe we're falling for it again. I really can't. Because there's nobody making money on it, it's peculiar that it has a literature that's still active. But it's not going to help us, and let's not wait for it.

The last thing is in terms of oral antibacterial drugs, the only thing the clinicians care about is bioavailability. The reason for the quinolones' phenomenal success is really not so much their spectrum, in my opinion, as the incredible bioavailability. The problem with them is everybody's popping Tums still or is on magnesium for something, and there are binding issues.

So if we knew that something had really good bioavailability, we would love it. That to me is the -- we actually listen -- clinicians actually listen to evidence once in a while.
DR. MOORE: Thank you. Ms. Young?

MS. YOUNG: I agree with what everyone said in terms of to have a valid study, we should exclude the population that has received prior antibiotic therapy. And in terms of enriching the microbiologically intent-to-treat population, I would say we should use all the methods available, molecular PCR, urinary antigens.

I thought Dr. Bartlett's presentation that we need to move forward with rapid diagnostics is really at the heart of this whole discussion, whether you're talking trials or appropriate treatment. And so I think that these trials should get a bonus if they actually are using some of the new diagnostic methods because we'll learn something from that.

In terms of whether we need to do these trials in the U.S. or overseas, maybe it's better to do them overseas where they're not overusing the antibiotics quite as much. I'm not sure.

In terms of facilitating the trials, I thought there were some suggestions this morning
about the emergency department, 24/7, having somebody based there. Consent forms, definitely, if there's a way to have a short form first. And then the CMS guideline, I think it'd be great if IDSA could speak with CMS and tell them that this is a perverse incentive and work something out so that the standard of care becomes better at the same time as the standard of the clinical trials.

Thank you.

DR. MOORE: Thanks. Dr. Weinstein?

DR. WEINSTEIN: With regard to prior antibacterial therapy, ideally, I'd prefer also that there be no prior antibiotics. But that having been said, if that would make it a complete non-starter to do clinical trials in the U.S., I guess I would consider, reluctantly, one dose of a short-acting antibiotic.

With regard to item B, enriching the micro-ITT population, I simply can't be that optimistic. And I'm saying that both as an ID clinician and as a director of a microbiology laboratory.

Think about it for a minute. What
laboratory tests are reliable for the diagnosis of community-acquired bacterial pneumonia? A positive blood culture, a positive culture from empyema fluid, a pneumococcal urinary antigen, a Legionella urinary antigen, probably a sputum culture, growing strep pneumo in a patient who has a Gram stain that is compatible with that and a pulmonary infiltrate. And maybe you could say the same thing for a Gram-negative rod.

We have no idea what the clinical significance is of finding microbial DNA from a virus or bacteria in a respiratory specimen. We don't know what the clinical significance of that is. Does that represent the organism being a pathogen, or is that organism simply there as a colonizer? We don't know. And I'd submit that Johansson didn't know.

So I think that to suggest that that kind of technology is going to make the difference in whether or not you can do more clinical trials is overly optimistic. And so I think that the agency needs to take that into consideration. It's
certainly technology that is worth studying. We need to learn more about it, and we need to know where it fits in our diagnostic armamentarium, but I don't think we're there yet.

Procalcitonin. I agree with you, and it also doesn't provide an organism, so I don't know how that enriches the micro-ITT population.

So while I'm on my curmudgeonly rant here, what about overcoming barriers to clinical trial conduct? From my perspective, IRBs and HIPAA regulations have become impediments in trying to enroll subjects in clinical trials and to do clinical research altogether. Indeed, these roadblocks have become a major headache and a disincentive to doing clinical research.

DR. MOORE: Thank you. Dr. Cappelletty?

DR. CAPPELLETTY: With regard to the prior antibiotic therapy, I agree we have two arenas that we're dealing with. And with the changes with CMS, will we see some changes with the ED in terms of loosening up and not starting antibiotics as quickly?
With regard to the patient coming from home, having taken an antibiotic that was either priorly prescribed recently or long ago from their primary care physician, that's a significant issue. Consistently, in the top 200 drugs that are not only prescribed but dispensed in the United States, amoxicillin ranks, usually, in the top two to three. And last year it was number two.

Azithromycin is usually in the top 20, usually in that, somewhere between 12 to 15 range. And again, last year, it was number 15. It came up again in the number 20s, depending upon which generic company is out there.

So we have a broad use of antibiotics in the community setting that are always going to continue to influence and play a role here that is going to be difficult to eradicate. And when you have a patient who's failed their amoxicillin or azithromycin therapy and now are presenting with a more severe form of disease or a prolonged duration of disease, you're changing the baseline characteristics of that patient that's being
enrolled versus the patient that has just presented
with a couple of days' symptomology. And you're
potentially changing those clinical response times
as well with that.

So I have an issue with that prior
antibiotic therapy, and I also have an issue with
what has been called, at least in one of the
presentations earlier today, short-acting drugs in
that they included tetracyclines as a class, which
the only drug in that class with a short half-life
is tetracycline. Minocycline and doxycycline both
have half-lives in excess of 15 to 20 hours, so a
single dose there is going to highly impact on the
outcomes there. And they also included
trimethoprim-sulfamethoxazole in that arena, and,
again, 10 hours for each of those agents is still a
relatively long half-life.

So I have concerns with what's being defined
as a short-acting drug, that a single agent could
have some significant role there. So I'm in favor
of, again, the cleanest trial design would be no
prior antibiotics if at all possible.
I don't have much to add in terms of enriching the micro intent-to-treat population, but as Dr. Reller said, the urinary antigen test sort of persists for very long periods of time. And so how are you going to establish a microbiological response? If you're using that to include in a role, you would have the increased microbiologic initial, but what's going to be the outcome that is going to be based for the cure.

So if that antigen persists, is it going to be called a microbiological failure, or is that going to be called a cure because, symptomologically, the patient got better? So there are going to be some apple and orange mixes there with some of that.

Barriers to overcome trial conduct, I think they've been well talked about, and I don't have anything to add there. And advice on oral antibiotics, again, looking very closely at the kinetics of the drug would be very much required. And I think organizing clinicians in the outpatient setting for trial study, trial design, and
networking community practitioners is going to be required to make them effective. And any preliminary studies looking at lung concentrations would be of benefit as well to ensure that you're going to have some degree of success.

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

DR. D'AGOSTINO: I have little to add, but I'll make a couple of comments with regard to A and C. The less prior antibacterial therapy, obviously, the best you could do, and the less is the best. And if there's none, that's super best.

You can handle these things by stratification of analysis, but I think it may be a dead issue, that if there's too many already on prior therapy, that you're going to ruin your study. There may be a possibility with the relaxing that we heard about this morning, that people will hold back on that. But unless that does happen, I think that it's going to really be a problem. And taking studies out of the U.S. may, in fact, be the way it's going to be resolved, that you can't run these studies in the U.S. because of
the prior therapy.

I had a study where we had to go to Peru to look at respiratory distress because you just couldn't run them. And when you went to Peru, these things weren't available, so there was a real bonus to the other countries, and that's an inducement.

In terms of inducement for getting people into a non-inferiority, the game I've always seen in terms of studies I've been involved with is that there's a benefit to the non-inferiority. It may not be efficacy, but side effects and other things. And I don't know if you have that type of play that you have here, that there's going to be something better. It doesn't sound like it.

In terms of doing these type of studies, I've done a number of studies in emergency rooms, and it's really an organization problem in order to get it. There's a lot of competition for studies. There's a lot of concern about patients being treated and what have you. You have to have, basically, a person assigned to there. You can't
say to the center, we'll pay you part of a salary for somebody. You have to really figure out how you're going to be able to fund this, that people down there are available to run over to these patients.

I've done cardiac and people are holding their hearts, thinking they're going to die, and they still sign the consent forms because the consent forms become a lot less hard to deal with. There's this dedication in terms of the staff. And you have to do these things. You just can't add another burden to the emergency room or other settings and say, add this study. You really have to address these organization problems and these consent problems.

DR. MOORE: Thank you. Dr. Bennett?

DR. BENNETT: I have nothing to add to what I said before, but I have a question for Katie Laessig.

Does the FDA know how often it might be that a person who's entered in a community-acquired pneumonia trial on the basis of an x-ray, which is
required to have an infiltrate, a review by another radiologist would not be able to confirm that?

The reason I ask that question is, first, we know that all the radiology in this country is being stored electronically. And electronic storage has become very cheap, so it would be relatively easy to retrieve these records if it was worth the time.

I also know that now that we're getting CTs of many patients, what we thought was an infiltrate doesn't turn out to be so on a CT. I also know that radiologists differ. So it may be a stupid question that never needs to be answered, but do we have any idea as to how often these can't be confirmed?

DR. LAESSIG: The short answer is no, not off the top of my head. But, yes, and as you'll hear tomorrow, that's been an issue for HABP trials as well, is that there's inconsistency with interpretations for chest radiographs.

DR. MOORE: Thank you. Dr. Masur?

DR. MASUR: I guess I'm one of many people
here who wish the data were different. I mean, I wish that one dose of antibiotics did not make such a big difference, I guess, as opposed to Tom, who's looked carefully at the data, I'm surprised that one dose makes such a difference. And it's clearly an important clinical question. Once somebody's gotten a dose of antibiotics, how should you treat them? But that's not really what we're here to address.

So I wish I could say that I'm in favor of patients enrolled, regardless of antibiotics, but it's hard to look at the data in favor of that perspective. And I hear what John Rex and others have said, how difficult these studies are going to be. People have said that we need to fix the regulatory and the operational issues.

I think the ACTGs probably have recognized what the issue is here, that this is not going to succeed unless there's somebody in the ER many hours a day, who is waiting at the door each time a patient comes in, saying I'll take charge of making sure this patient is offered the trial, and
I guess we all wish that life were different, but it's not.

DR. MOORE: Very good. Thank you.

Dr. Wiedermann?

DR. WIEDERMANN: Thanks. I would really on A have to defer to my internist colleagues, but I'm pessimistic that removal of the CMS rule is going to change practice by internists and emergency medicine physicians overnight, because I think part of this was happening well before the CMS rule. But, again, I would defer to them.

I guess I would, from a logistical standpoint, still favor allowing enrollment of patients who have received short-acting, truly short-acting, referring to Dr. Cappelletty's comments, antibiotics, but maybe supplementing that with something like a urinary bioassay so that maybe with a preplanned subgroup analysis, there could be some guess as to whether there was a correlation with the urinary bioassay and duration of symptoms, or something like that, where you can
get a feel for how important it was, beyond just, they did or didn't receive it.

In terms of B, two years ago, my institution made available a multiplex respiratory viral PCR in the midst of the H1N1 panic. And I would have to say, at least subjectively, it's probably done more harm than good at our institution, creating all kinds of excessive expenditures.

With that, though, I think it's still worthwhile trying to do something like that because we basically don't know what these tests mean, how long they persist positive. And, again, if we're collecting some of this information at the time of enrollment, maybe with, again, preplanned analyses, we can make a little sense out of it, still unlikely with just a trial or two to come up with the answer.

Barriers to trial conduct, that's how I lost all my hair, so I don't know that I have anything to add beyond what's been said. And then in terms of the oral antibiotics, I would just wonder whether this is a place where pharmacometrics can
help us in particular if we get some information from IV trials. I have to say I'm one of the Doubting Thomases with pharmacometrics, especially vancomycin and staphylococcal disease, but I think that might be a tool that could make oral trials a little more understandable.

DR. MOORE: Thanks. Dr. Calhoun?

DR. CALHOUN: With respect to receipt of prior anti-bacterial therapy, that I think is probably the thorniest of all the issues that we're dealing with today, save the very first one, which was the outcome measures.

The data that have been presented suggest that a single dose of a short-term, short-acting antibiotic minimally affects the outcome. As I think everyone has said, the best experimental design, the best inclusion/exclusion criteria, would be to exclude everyone who has had a prior dose.

I do think that it would be disadvantageous for us nationally, the agency specifically, if all of our registration trials for community-acquired
pneumonia were conducted offshore. I just don't think that that's a good thing.

So maybe we need to develop a list of acceptable short-actings -- I think Dr. Cappelletty was on the mark here -- a list of short-acting antibiotics that would be okay, would be non-exclusionary. But I think there has to be some way forward in which a single dose of a short-acting antibiotic would be acceptable. If it could be dealt with, as Dr. D'Agostino mentioned, by stratification, or some other statistical methodology to pull that out, I think that would be a benefit.

Vis-a-vis the enriching of the micro-ITT population, I think Dr. Follmann hit this on the head. This is all about population characteristics. It's not about individual characteristics. And so the best predictor probably is going to be the severity of the disease as it presents.

If molecular methods could be provided with a turnaround time that would actually work -- and I
think that's going to be 60 to 90 minutes or
less -- so they would actually function as a point
of care test, then maybe a molecular method,
whether it's chip based, a PhyloChip, or something
like that, or a semi-quantitative PCR method to get
to the question that was raised earlier as to
whether simply detecting DNA or RNA from a
pathogenic bacteria represents infection or not.
So maybe you could do that with semi-quantitation.

Vis-a-vis the barriers, the key things have
been mentioned. It's infrastructure,
infrastructure, infrastructure. You've got to have
the people in the ED, and I think that probably is
the proper site to conduct the trials.

What that means is that these are going to
be expensive trials because it's essentially two
shifts per day, seven days a week. So if you're
budgeting out a trial, that's two FTEs plus your
vacation and all that other stuff, per year of the
trial. That's a lot of money. So they're going to
be expensive trials in addition to all the other
expenses that are put into the mix.
Vis-a-vis the regulatory barriers, there may be barriers with respect -- it's not been mentioned, but investigational drug services are sometimes part and parcel of the experience at academic institutions. And they're notoriously unhelpful in getting a drug quickly to a site that might need it, like an emergency department. They might take six hours to get you your drug, and that's clearly not helpful.

It does seem to me that the agency has an opportunity, once again, to take a leadership role here in developing some model consents that could be vetted through OHPR and other human subjects, agencies, to facilitate the acquisition of consent in the emergency department. Our consent forms, like most of those that have been discussed, approximate 20 pages for simple things and for things that include bronchoscopy might be 25 or 28 pages.

So a simple consent form, if we can in fact learn -- as Dr. Temple mentioned, if we can learn from the successes of the cardiovascular folks with
early intervention, the stroke folks with early
intervention, if we can learn and model some things
with respect to pneumonia, that may actually be
helpful.

Then, vis-a-vis D, I would reframe the
question or at least add to the question, when a
formulation is not available or in fact not
necessary. There are many people who we see in the
outpatient clinic who have got clear lobar
pneumonia who don't need to be hospitalized. They
can go home with oral antibiotics.

So I would just expand the thinking about
CAP that may well include a big subset of
ambulatory people, particularly younger folks. A
35-year-old with lobar pneumonia probably doesn't
need to be hospitalized.

DR. MOORE: Thank you. Dr. Shyr?

DR. SHYR: Again, the focus is on how to
interpret the result, back to question number 1.
Sure. I agree, the prior antibiotic therapy;
definitely clean, better, especially when we are
doing these non-inferiority trials. So this really
cannot be ruled out if we include those patients, have a carry over residual effect, which makes the results very hard to interpret.

However, we cannot ignore how hard we can get a patient here in the United States. We see a majority of patients internationally, especially a third-world country. I share one story with you. I visited China the other day. I didn't feel well. My friend opened a drawer. He has about 20 different antibiotics there. So you pick the one. I mean, if you don't feel well, you just take that. So when we get the data, they say I did not have antibiotic before, how reliable is that data? So we have to make sure. Again, we run the non-inferiority trial, the quality of the trial -- the quality of the study is essential.

So if we have to include those, so the patient has prior antibiotic treatment, then we need to know -- back to stratify. I think the pharma need to understand the risk of doing that. After you stratify the patient, if the results are inconsistent, back to my original concern, it's not
interpretable.

So leaning to, if we can do a pure study, sure, we should do that. If we really cannot get enough high quality data; we need to know the price we have to pay.

Secondly, as we talked about, is there another way we can enrich? I think maybe it's the time the FDA, NIH can come out with some kind of RFA to encourage the people, the small company, can they do something better. I know it's not easy, I learn all them, the biostatisticians here. But I do think, at this time -- even I was told the other day, they are doing flow cytometry technology again, up to 25 colors, major 1.5 million cells per second. I think there are a lot of those fancy stuff, people are thinking. Maybe the federal government can encourage something to really improve this area. But, again, micro-ITT is our goal we want to get at.

I couldn't agree more, how hard to run a trial in the ER. I have a colleague who's a junior faculty in our institution. Around a year, our
trial ends up -- we threw out the entire three
months of the data because he was on vacation. The
people did not follow the protocol clearly because
of the ER environment. So I think we should do
whatever we can to help the people run,
including -- everybody say the consent form.

Is there any way we can do that, help the
people run that?

I don't have any comment for question D.

DR. MOORE: Thank you. Dr. Rex?

DR. REX: Thank you. A lot of good
comments. On prior antibiotics, I have a little
extra data on feasibility, shared with me from
David Friedland, that I think might be helpful.
David's already commented that they had two
challenges to their U.S. enrollment, the first
being the general U.S. preference for a macrolide
knocked the number of sites interested down by more
than 90 percent. And then the second problem with
the remaining sites found prior antibiotics were a
real issue. And the thing I want to add is why
David said that it was an issue.
The reason is that a typical site enrolls about .4 patients per month, which means that you enroll about 1 patient every two months. If you look at the ceftaroline trial program, about half the patients had had a prior antibiotic. So if you exclude the ones who had had a prior dose, you're now down to enrolling one patient every four months. That's a long time for your study nurse to sit around not enrolling patients, and that's a significant cost and loss of interest.

So that's theme A. Theme B on this is that I do want to point out the trade-offs involved in permitting enrollment with any prior antibiotics, even a short dose. So I'm going to end up concluding that we need to permit it, but I do want to point out some trade-offs.

The key trade-off is rather like the early/late endpoint trade-off. If a sponsor chooses to enroll some patients who have had prior antibiotics, there will be a secondary or sensitivity analysis done to examine the effect of those prior antibiotics. Guaranteed, right?
Sponsors must recognize that on the up side, this analysis might show only a consistent effect across the arms, and if it did that, then you'd say, fine, it didn't actually mess anything up.

But there's a downside risk. The downside risk plays in two ways. One possibility is that a prior antibiotic might obscure the superiority of a new agent. We actually saw that in one of the two ceftaroline trials. It actually blunted a little bit of the trends toward numerical superiority.

The other thing is the analysis might suggest that the prior antibiotic has partially masked an effective agent. So that's a problem as well.

Tricky. This could occur even by chance because you're starting to get into subsets. Subsets always have a higher risk of sort of a deviation from the central tendency, just by chance, so that's a risk for the sponsor. So a wise sponsor should, and would I think, choose to limit the proportion who enroll with a prior antibiotic so as to ensure that chance variation doesn't wreak havoc.
I should say why a sponsor would really work very, very hard to reduce prior antibiotics, but nobody has commented on whether there might be an upside of enrolling at least a few of these patients. Actually, there probably is a little bit. My thought here is that enrolling them would help ensure that you don't exclude important populations, such as those most critically ill and who is most likely to get a prior antibiotic on their way to being sent to the emergency room out of the physician's office. The other important population that it means you can accrue is, of course, those who live in the United States.

So, in summary, I think we end up needing to permit a sponsor to choose to include a fraction of subjects who have received a very brief course of a prior short half-life antibiotic. It's the sponsor's risk, but I think it needs to be permitted.

The effect of this appears to be small and it seems unlikely, based on what we know, that permitting such short -- it's probably one dose of
something. It seems unlikely that would allow an ineffective agent to escape detection. That's the real concern, is that we'll miss -- is that we will fail to detect an ineffective agent.

I think, based on what we've seen, even daptomycin was picked out quite handily, and daptomycin is not an ineffective agent. I mean, you recognize that it works everywhere but in the surfactant. It works in the tissue, and it works in the blood, and yet that study picked it out quite handily.

Micro-ITT, any tool that enriches would be fabulous. And there's actually a lot of work underway on this, but, unfortunately, little of it is ready for primetime. There was a workshop held about two weeks ago, jointly sponsored by the European Commission and NIAID, that was driven in part by the Transatlantic Task Force for Antimicrobial Resistance, a very nice outcome of TATFAR, that showcased a lot of the work that's been spun up over the past few years in rapid point-of-care diagnostics.
There's some pretty neat stuff coming. And so I have to emphasize the word "coming." The bus has not yet pulled in, but it's on its way. And when those things become available, I think we're all going to want to use some of them. But right now, I've got to do trials, and I can't wait for one of these things. So I'm kind of with Mel Weinstein. It's not happening yet.

I don't have much to add about barriers. And, finally, oral drugs, we have to make it feasible. And the approach based on a mixture of PORT II, III seems feasible. It looks like it ought to be.

I do need to think further about the required level of baseline physiologic derangements. As has been noted, those are pretty strong requirements, and some of those things are you're kind of halfway to the ICU if your respiratory rate is that high and if your blood pressure's that low. So we'd have to look hard at that.

I would say that we've spent a lot of time
talking about how bad PORT II is and that it isn't a very strong finding. Remember, we're talking about microbiologically proven disease. Anybody who has the pneumococcus in their sputum and has a pulmonary infiltrate, they're going to have to pass through a stage where they're PORT II, before they get to being PORT III, before they get to being PORT IV. So the fact that you happened to catch them before they were in the ICU is the good news. It doesn't mean that they will continue to deteriorate.

You read the classic papers from Osler, and it's very clear that patients go from feeling a little bad, to a little worse, to really, really, sick, sick, over the course of two or three days. So the fact that you caught them at PORT II doesn't mean they're not on their way to PORT III, and I think that's worth recognizing.

So I truly believe that microbiologic proof is a big help in this area, and I'll stop there. Thank you.

DR. MOORE: Thank you.
Dr. Cox, you wanted to say something before we adjourn?

DR. COX: Well, two things. I wanted to first start out by thanking Dr. Sepkowitz for his service to the committee. He's been on the committee for three years, and this completes his three-year term, and we're grateful for your commitment, your diligence, your service, coming and joining us.

We recognize, too, that it's not simply the time that you spend here with us and in travel, but there's also a tremendous amount of time spent before you get here, working through all the issues.

So Dr. Sepkowitz, we thank you and we're grateful for your service.

DR. MOORE: Here, here.

[Applause.]

DR. COX: Then if we're at the point that we're about ready to wrap up, I just want to thank the committee members and all the speakers today, too, for their comments. We tremendously value the
advice we get at these meetings, and we very much appreciate the thoughtful comments and all the work that folks do. So thank you very much for joining us today and for all of your work. We appreciate it.

Adjournment

DR. MOORE: I want to thank the FDA as well for all their hard work, everybody. This will conclude the session today.

Could the meeting participants please leave their name tags at the table for tomorrow, which will be hopefully shorter, but just as intense, I'm sure. Thank you, everybody.

(Whereupon, at 5:20 p.m., the meeting was adjourned.)