Statistical Issues Think Tank II

Executive Summary of the Expert Meeting Held November 19, 2014

Bethesda North Marriott Hotel & Conference Center, Bethesda, MD

CTTI MISSION: To identify and promote practices that will increase the quality and efficiency of clinical trials

Meeting materials, including agenda, participant list and presentations, are available on the Clinical Trials Transformation Initiative (CTTI) website at: https://ctti-clinicaltrials.org/statistical-issues-think-tank-ii/

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MEETING OBJECTIVES

The goals of this meeting were the following: to provide an update on the current status of statistical methodologies for the design and analysis of antibacterial drugs; to discuss ongoing challenges in the development and adoption of innovative methods; and to generate strategies to propel antibacterial drug development forward.

MEETING EXECUTIVE SUMMARY

On November 19, 2014, the FDA's Antibacterial Statistics Working Group convened a meeting of statistical and medical experts in the area of antibacterial drug development. The meeting participants represented a variety of institutions: regulatory; pharmaceutical; NIH; academic; contract research organization; and independent consultants. Prior to the meeting, participants received several publications; a number of these formed the basis of presentations throughout the day. In her opening remarks, Dr. Lisa LaVange, FDA, highlighted her expectations for the meeting and provided an update on work that has been completed since the first think tank in August 2012. After the opening remarks, Dr. Dionne Price, FDA, led two moderated sessions, each of which began with a series of presentations and concluded with an open discussion. The first session focused on the current status of antibacterial drug development and its associated statistical design and analysis challenges. The second session was more forward-looking than the first. It focused on innovative statistical design and analysis approaches that may be useful in the context of emerging resistant pathogens and small patient populations. For both moderated sessions, participants directed their comments in response to prepared discussion questions. This summary highlights the key points from the opening remarks and the two moderated discussions.

After enumerating the many statistical challenges of antibacterial drug development, Dr. LaVange expressed her desire that the day's meeting would continue to advance regulatory-industry collaboration as there is still much work to be done. In her presentation, Dr. LaVange identified a number of statistical considerations that make antibacterial trials particularly challenging: enrolling participants who require immediate care; establishing non-inferiority margins; defining analysis populations from microbiology results; and limited numbers of patients. Responding to the need for relevant external data and improving trial efficiency, Dr. LaVange offered a solution borne out of FDA-NIH collaboration, a trial network with a common protocol and data sharing. Other innovative ideas emerged from the 2012 meeting: imbalanced randomization; cluster randomization; nested trial designs to leverage all patients' data; and borrowing information from external control subjects and infection sites. Two of these innovative ideas, nested trial designs and Bayesian approaches to borrowing information, are actively being researched at the FDA; these would be discussed

further in the moderated sessions. Acknowledging that all of these innovative ideas are signs of progress since 2012, Dr. LaVange reminded participants that much work remains — especially in the area of resistant pathogens — to reduce the time and cost of development of antibacterial drugs.

The goal of Session 1 was to understand the current status of antibacterial drug development and the ongoing challenges in the design and analysis of development studies. The first part of the session comprised four presentations on the current regulatory standards and guidance documents, pharmacokinetics-pharmacodynamics (PK-PD), and considerations for a tiered approach to drug development. The session chair, Dr. Dionne Price, FDA, invited meeting participants to review three discussion questions and keep these in mind while listening to the presentations. Following the presentations, the second part of the session was a moderated discussion framed around three discussion questions.

One point for discussion was how preclinical evidence could be incorporated into the analysis of confirmatory trial results. A number of participants agreed that PK-PD relationships *in vitro* or in animal models are very informative. However, there were a number of concerns about how these data should be applied to human experience. For one, extrapolation from animal models to humans requires assumptions: It is preferable to have actual data than priors. Another caution is that some anti-infective drugs have failed in clinical trials despite well-characterized PK-PD relationships. Although there may be uncertainty about the strength and consistency of the relationship between PK-PD and clinical efficacy, the PK-PD data could still be incorporated into the prior information. Another concern was that a single approach to this question may not be advisable; instead, a variety of approaches could be entertained based on the prevalence of pathogens or body sites. Overall, a number of participants agreed that PK-PD relationships could be incorporated with clinical efficacy using model systems and were best viewed as information about delivered dose in humans.

Another discussion point for the session was the potential role in anti-infective drug development of single arm trials. Without randomization, single arm trials rely on external control data. A number of participants stated a strong preference for studies that included randomization, even if to a small concurrent control group or to maintenance therapy. In some instances, randomized arms might be dropped adaptively. Although recognizing the need for external control data, participants identified a number of challenges with its use: external data are not always collected in a standardized fashion; it may not always be clear how to weight internal and external controls; and cure rates may drift over time, especially for pathogens with emerging resistance. Many of the concerns about external data could be mitigated by using a common protocol and standardized prospective data collection; it would be possible to assess temporal trends and estimate covariate-adjusted cure rates. For trials using external control data, sponsors could simulate clinical trials to describe the study's operating characteristics. With an understanding of the operating characteristics, the

sponsor would seek mutual agreement with the FDA on the study design. Overall, participants agreed that relying on external control data is less than ideal. However, the evidential quality of such trials can be bolstered by using clinical trial simulation and standardized data collection.

The final discussion point was how a master clinical trial protocol might be used to evaluate anti-infective drugs. The idea of a collaborative network with a common protocol has been proposed in oncology; participants were asked to comment on its utility for antibacterial drugs. Participants offered a number of advantages of the master protocol including the following: data from control patients could be shared across studies; data collection would be standardized to enable evidence synthesis and tracking temporal trends; and a common protocol would readily accommodate group sequential methods. Multiple participants noted that a master protocol was a necessity for combining evidence across controls. It was also noted that existing data sources do not include microbiology data and use their own data standards. Although there was resounding support for the concept of the master protocol, there was some concern that sponsors may be reluctant to contribute data if their products may be compared to a competitor's.

The goal of Session 2 was to review current methodological research and generate strategic research ideas for the future. The format of Session 2 was similar to Session 1; an open discussion followed four presentations. The first two presentations described novel approaches to nesting superiority and non-inferiority in the same trial. Combined endpoints for safety and efficacy were proposed in the third presentation. The fourth presentation included proposed Bayesian approaches to the analysis of antibacterial trials. During the moderated session, participants offered their thoughts on the prepared discussion questions.

When antibacterial agents are associated with significant benefits and toxicities, a traditional non-inferiority approach for efficacy may be difficult to interpret. An alternative approach, RADAR, combines benefits and harms into ordered categorical responses that may then be tested for superiority of a new agent to an active control. A superiority design eliminates the need for justifying a non-inferiority margin and likely requires a smaller sample size than non-inferiority designs. Participants noted the following additional advantages of an approach like RADAR: it demands a more thoughtful process about what to measure; it highlights benefits that may only be implied from traditional designs; and it avoids the difficulty in assigning explicit weights to individual outcomes. Although many participants voiced support for an approach that combined benefits and harms, they indicated that it may be difficult to order response categories in some situations.

On the issue of Bayesian approaches to design and analysis, participants cited flexibility and incorporation of key uncertainties as key advantages of Bayesian methods. Participants were enthusiastic about the utility of Bayesian methods at

the design stage. For example, they can be used to estimate the probability that power is at least 80%. Another advantage of Bayesian methods is their flexibility in ongoing data monitoring; framing minimal efficacy thresholds as a probability statement may be more informative earlier than traditional approaches. Another advantage of Bayesian methods is that they can be used to integrate benefit and risk. A number of participants stated that Bayesian approaches are quite useful to augment controls when sample sizes are limited.

While there was agreement about the advantages of Bayesian methods in design and analysis, there were mixed opinions about proposed analysis strategies for studies of infections at different body sites. Several participants expressed the opinion that borrowing data across sites was most appropriate for tests of superiority. Others voiced the concern that significant variability from site-to-site would adversely affect the analysis: patients with infections in different sites are dissimilar in other ways that may affect results; and variability would limit the amount of information borrowing and therefore not address the problem of limited sample size. Although some participants were more cautious about these methods, others — citing recent experience in oncology — had a more favorable view of the potential of using hierarchical models to borrow information across sites. The models are similarly motivated out of necessity for larger sample sizes, but data are only borrowed when there is evidence of homogeneity. Use of the hierarchical models could be enabled by a master protocol and standard database; the data could be queried to evaluate if one site predicts another. Although the proposed Bayesian hierarchical modeling approach has strengths and weaknesses, sponsors proposing to use it should describe its operating characteristics using simulation.

Before the meeting was adjourned, participants were asked to identify future research priorities. Multiple participants cited the master protocol and trial network as a priority. Other ideas included the expanded use of simulation to study operating characteristics, network meta-analysis as an alternative to traditional approaches to defining non-inferiority margins, and approaches like RADAR that combine benefits and harms into a single ordered outcome.

Dr. LaVange expressed her gratitude for the input of the meeting attendees and adjourned the meeting.

FUNDING STATEMENT

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ABOUT CTTI

The Clinical Trials Transformation Initiative (CTTI) is a public-private partnership to identify and promote practices that will increase the quality and efficiency of clinical trials. The CTTI vision is a high quality clinical trial system that is patient-centered and efficient, enabling reliable and timely access to evidence-based prevention and treatment options.

For more information, contact Matthew Harker at matthew.harker@duke.edu or visit http://www.ctti-clinicaltrials.org.

Appendix A. Meeting Agenda

Meeting Agenda
Wednesday November 19, 2014
9:00 AM-4:00 PM

8:00-9:00 AM	**Registration/ Breakfast**
9:00-9:20 AM	**Welcome and Opening Remarks: Lisa LaVange, PhD** Director, Office of Biostatistics, OTS/CDER/FDA *Session goal: Understand the objectives for this meeting and summarize the discussion and advances since the first CTTI statistical issues think tank in August 2012.*
Session 1 9:20-10:20 AM	**Current status of drug development and ongoing challenges** **Session Chair: Dionne Price, PhD** Director, Division of Biometrics IV, Office of Biostatistics, OTS/CDER/FDA *Session goal: To understand the status of antibacterial drug development and the ongoing challenges in the design and analysis of antibacterial drug products* **Presentations** **Joseph Toerner, MD, MPH (10 min)** *Office of Antimicrobial Products/CDER/FDA* *Brief Summary of Regulatory Standards and Guidances* **Dan Rubin, PhD (15 min)** Mathematical Statistician, Office of Biostatistics, OTS/CDER/FDA *Summary of the Unmet Need Guidance and Statistical Challenges* **Seong Jang, PhD (15 min)** Reviewer, Office of Clinical Pharmacology, OTS/CDER/FDA *Application of Pharmacokinetics/Pharmacodynamics in New Anti-Infective Drug Development: Current Challenges and Future Perspectives* **Aaron Dane (15 min)** *Biometrics & Information Science, Infection TA Head, AstraZeneca* *Statistical Considerations for a Tiered Approach to Antibiotic Drug Development* **Questions and Answers on presentations**
10:20-10:30 AM	**Break**

10:30-12:00 PM **Moderated Discussion**

Discussion questions:

1. What concerns exist regarding incorporating preclinical evidence into the analysis of confirmatory trial results? What analyses techniques might be appropriate for incorporation of preclinical data?

2. Is there a role for single arm trials in evaluating anti-infective drugs? If not, what are viable alternatives to single arm trials? Discuss possible strategies aimed at leveraging external data in development programs in potentially limited populations.

3. Discuss considerations involved in using a master clinical trial protocol to evaluate new anti-infective drugs.

12:00-1:00 PM **Lunch**

Session 2 **Current research and additional opportunities for the future**
1:00-2:15 PM

Session Chair: Dionne Price, PhD

Session goal: To review current methodological research and to generate strategic research ideas for the future

Presentations

Erica Brittain, PhD (15 min)
Deputy Branch Chief, Biostatistics Research Branch, NIAID/NIH I
Discordant MIC Analysis: Testing for Superiority Within a Non-inferiority Trial

Thamban Valappil, PhD
Mathematical Statistician, Division of Biometrics IV, Office of Biostatistics, OTS/CDER/FDA
and
Mohamed Huque, PhD (15 min)
Senior Stat AdvisorOffice of Biostatistics, OTS, CDER, FDA
Hierarchical Nested Trial Design (HNTD) for New Antibacterial Drugs in Patients with Emerging Bacterial Resistance

Scott Evans, Ph.D, MS. (15 min)
Senior Research Scientist, Harvard University
RADAR

Margaret Gamalo-Siebers, PhD (25 min)
FDA
Proposals for the Analysis of Antibacterial Drug Trials

Questions and answers on presentations

2:15-2:30 PM **Break**

2:30-3:45 PM **Moderated Discussion**

Discussion topics:

1. Discuss the advantages and disadvantages of Bayesian approaches to design and analysis, and how a prior distribution would be chosen to analyze a confirmatory trial of an anti-infective drug. What would be some of the challenges and how might they be overcome?

2. Discuss evaluation of drugs posited to have similar efficacy profile to existing drugs but a superior safety profile. When can efficacy and toxicity measures be combined into a composite or ordinal endpoint to test for superiority, and when should a non-inferiority trial be conducted?

3. What are potential analysis strategies for a single trial enrolling subjects with infections at different body sites?

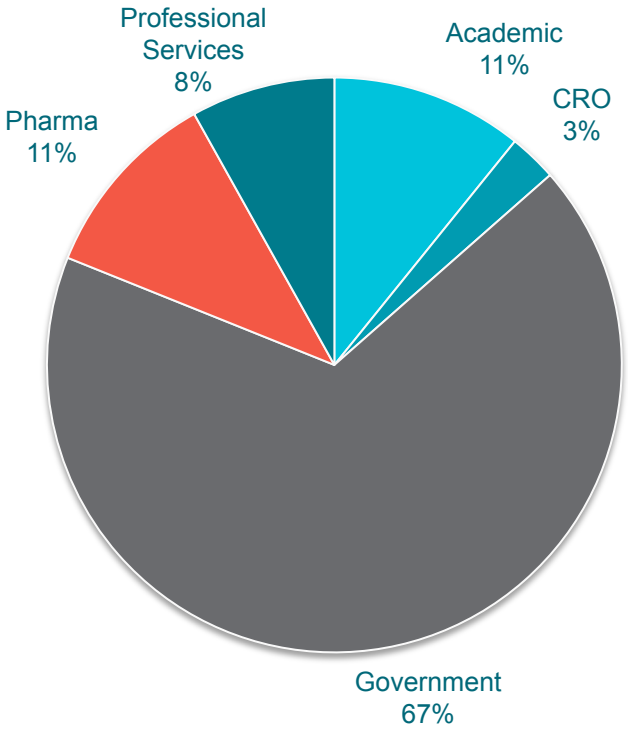
4. What additional opportunities exist for statistical innovation in anti-infective trials?

3:45-4:00 PM **Next steps and adjourn**

Appendix B. Meeting Participants

Our meeting participants include representatives from a broad cross-section of the clinical trial enterprise including regulators, government sponsors of clinical research, academia, industry, patient advocates, clinical investigators, and other interested parties. Participants are expected to be actively engaged in dialogue both days.

STAKEHOLDERS REPRESENTED



MEETING ATTENDEES

Amit, Ohad	GlaxoSmithKline
Ashton, Teri	GlaxoSmithKline
Bergman, Kimberly	FDA/CDER
Berry, Scott	Berry Consultants
Brittain, Erica	NIH
Campbell, Gregory	FDA/CDRH
Cox, Edward	FDA/CDER
Dane, Aaron	Astrazeneca
Das, Anita	Independent Consultant

Evans, Scott	Harvard School of Public Health
Farley, John	FDA/CDER
Gamalo, Meg	FDA
Guidos, Robert	FDA/CDER
Huque, Mohammad	FDA/CDER
Iarikov, Dmitri	FDA/CDER
Jang, Seong	FDA
Koch, Gary	University of North Carolina
Laessig, Katherine	FDA/CDER
Lavange, Lisa	FDA/CDER
Lin, Daphne	FDA/CDER
Little, Rod	University of Michigan
Louis, Tom	Hopkins University
Marchenko, Olga	Quintiles
Nambiar, Sumathi	FDA/CDER
Powers, John	NIH
Price, Dionne	FDA/OB
Reynolds, Kellie	FDA/CDER
Ruberg, Stephen	Eli Lilly
Rubin, Dan	FDA/CDER
Russek-Cohen, Estelle	FDA/CDER
Santiago, Jonas	FDA
Smith, Tom	FDA/CDER
Tiernan, Rose	FDA/CDER
Tiwari, Ram	FDA/CDER
Toerner, Joe	FDA/CDER
Valappil, Thamban	FDA/CDER
Viele, Kert	Berry Consultants

STAFF

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Sara Calvert	CTTI/DTMI	Leah Catherine Seaton	UMM
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