



Clinical Trials Transformation Initiative: Antibacterial Drug Development Project

Statistics Think Tank II

Lisa M. LaVange, PhD
Office of Biostatistics
OTS/CDER/FDA

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Outline

- Introduction
- General statistical considerations
- Statistical innovation in design elements
- Summary

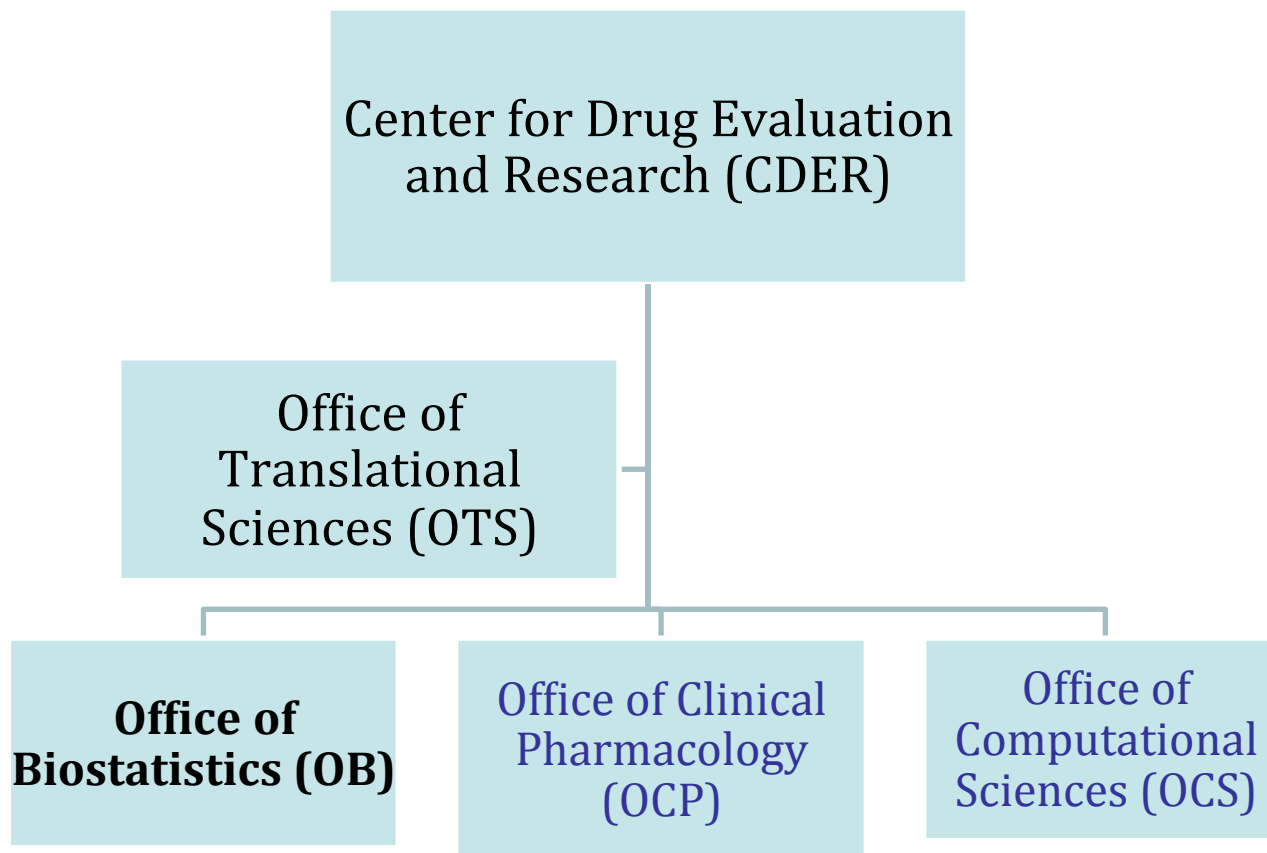


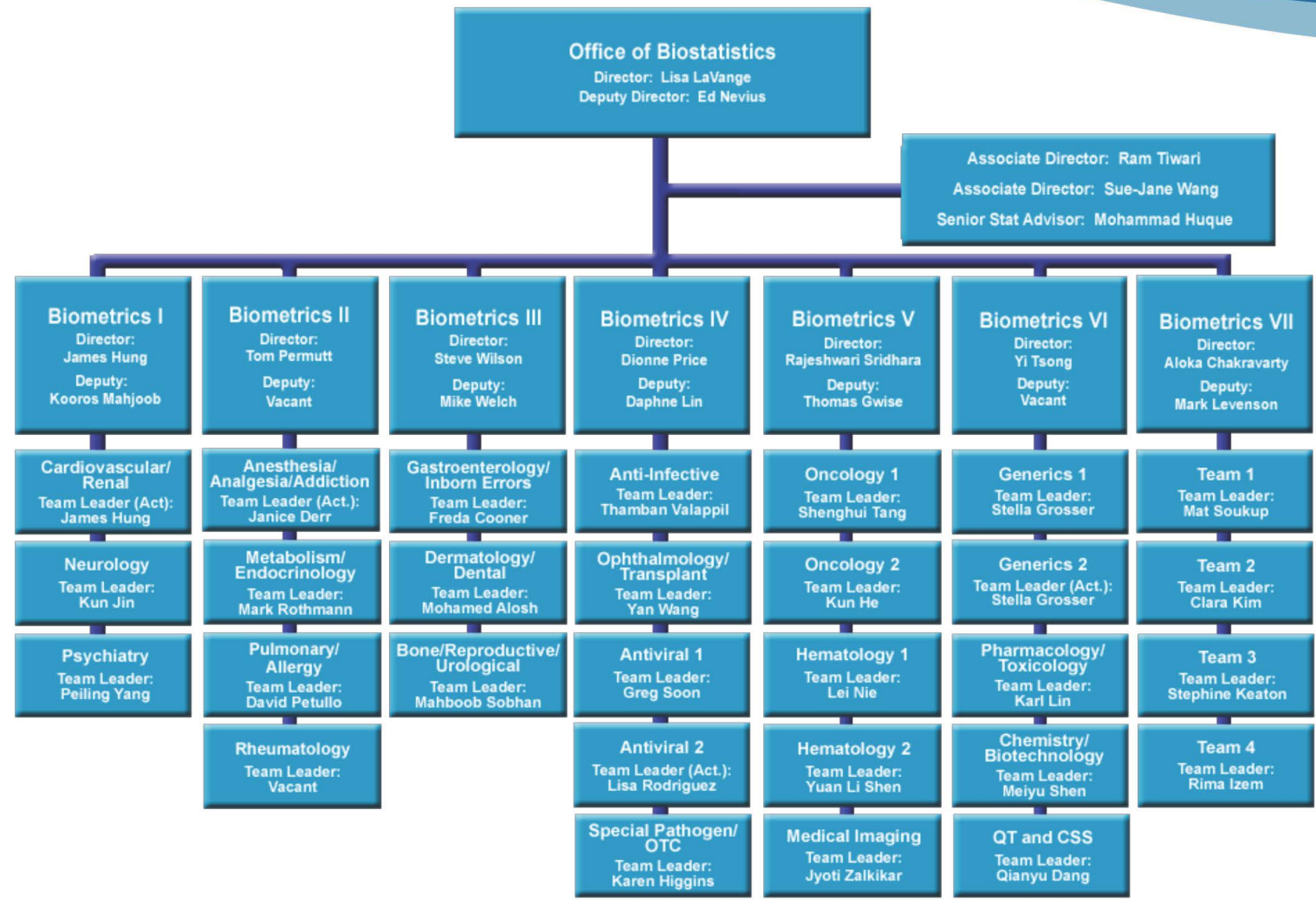
INTRODUCTION

Statistics and Anti-bacterial Development

- Anti-bacterial Statistics Working Group formed as a sub-committee of the CDER Anti-bacterial Task Force in 2012
 - Members from the Office of Biostatistics: immediate office and Division of Biometrics IV review team supporting anti-infective drugs
- CTTI Anti-bacterial Statistics Think Tank held in August, 2012
 - Panel of academic, industry, and government statisticians convened to discuss statistical innovation to accelerate or facilitate development of new anti-bacterial agents
 - Follow-up Think Tank meeting planned for fall 2014
- Several publications to date arising from the Think Tank discussion
- Many of the ideas in this presentation also stem from that discussion

CDER's Office of Biostatistics





Anti-Infectives Statistics Review Team

- Dionne Price, PhD – Division Director
- Daphne Lin, PhD – Deputy Director
- Thamban Valappil, PhD – Team Lead – Anti-Infectives
- Daniel Rubin, PhD – Statistical Reviewer
- Margaret Gamalo, PhD – Statistical Reviewer
- Christopher Kadoorie, PhD – Statistical Reviewer
- Mushfiqur Rashid, PhD – Statistical Reviewer

Additional members on Antibacterial Task Force Statistics Working Group:

- Ram Tiwari, Ed Nevius, Mohammad Huque, Joe Toerner, Kelley Reynolds, Kim Bergman



GENERAL STATISTICAL CONSIDERATIONS

Anti-bacterial Trials

Enrollment challenges

- Patients with serious infections present at clinical sites with an immediate need for treatment
 - Patients may be reluctant to agree to randomization
 - Administration of prior therapy is typically pre-randomization, so this is a problem of power (reduced ability to show efficacy) and not of bias
- Microbiology results not available pre-randomization
 - Most accurate estimate of treatment effect would be based on a comparison of patients infected with the pathogen(s) targeted by the drug
 - Use of a 'micro-ITT' analysis population does not induce bias but can impact power

Anti-bacterial Trials

Other design challenges

- Mortality vs clinical response endpoint—both carry difficulties
 - Mortality is more objective and may carry a power advantage, but co-morbidities can reduce power
 - Clinical response rate more appealing as direct measure of benefit but more difficult to ascertain objectively and consistently (across clinics)
- Non-inferiority trials when treatment with placebo is unethical
 - Margin determination can be challenging, if historical data not readily available
 - Quality issues of greater importance due to tendency for sloppiness to bias results towards a ‘no difference’ finding
 - Sample size requirements may be daunting in some infection types

Anti-bacterial Trials

Sample size (per arm) requirements to detect a difference between groups of 10% with $\alpha=0.05$ (2-sided) and 1:1 randomization*

1. CIAI and CUTI infections – clinical response outcome

Control Response	Power = 80%	Power = 90%
70%	330	442
75%	295	395
80%	252	337

*Source: CDER Anti-infectives statistical review team

Anti-bacterial Trials

Sample size (per arm) required to detect a difference between groups of 10% with $\alpha=0.025$ (1-sided) and 1:1 randomization*

2. HAP/VAP or Blood Stream infections – mortality outcome

Control Response	Power = 80%	Power = 90%
15%	200	268
20%	252	337
25%	295	395

*Source: CDER Anti-infectives statistical review team

NIH/FDA Initiative

Two approaches to address these and other challenges:

1. Establish a trial network with infrastructure in place to streamline trial logistics, improve data quality, and facilitate data sharing and new data collection
2. Develop a common protocol for the network that incorporates innovative statistical approaches to study design and data analysis



NIH/FDA INITIATIVE

Infrastructure advantages

- Streamlined enrollment procedures (e.g., NETT)
 - Need for prior therapy may be diminished
- Established systems in place to improve trial processes
 - Central randomization (e.g., via web portal)
 - Central electronic data capture system
 - In-network clinic personnel trained and experienced on existing systems
 - Study start-up time reduced
- Common case report forms (crfs) could help focus on critical data elements and minimize collection of less important items
 - Efficiencies realized during study conduct; data quality improvements

Infrastructure advantages

- Common elements of trial protocols can improve processes
 - Informed consent, clinical monitoring, data close-out, etc.
 - In-network clinical monitors trained and experienced on common elements
 - Efficiencies realized during study conduct; data quality improvements
- Centralized governance structure
 - Use of central IRBs, a standing DMC, and/or other bodies
 - Reduce study start-up time and provide ongoing efficiencies
- Central labs, reading centers, etc., with QA oversight
 - Some additional procedures required but improvements can be substantial in both data quality and reduced variability across clinics

Data Sharing

- Proposed trial network could encourage data sharing from studies conducted within the network, where appropriate
- Network could also facilitate new data collection
 - To aid in non-inferiority margin determination
 - As a source for prior information to support single study submissions or Bayesian approaches
- Chart data could provide perspective on past and current practices and patients, thereby informing future study designs
- Other types of studies could be conducted to support evidence from trials, e.g., case-control studies or retrospective cohort studies
 - Propensity score matching or other methods to control confounding



Office of Biostatistics, Office of Translational Sciences, CDER, US FDA

INNOVATIVE DESIGN ASPECTS

Prior Therapy

- Limit number of patients allowed on prior therapy, and stratify analysis
 - Could impose a tighter margin on the prior therapy stratum
 - Require trend towards superiority in the no-prior-therapy stratum (point estimate in the right direction)
- Should also confirm whether patient characteristics predispose those receiving prior therapy to achieve success

Imbalanced Randomization

- Alternative to single-arm studies in settings with significant recruitment challenges (e.g., resistant pathogens)
- Design includes an active control arm with highly imbalanced randomization (e.g., 2:1, 3:1, or higher)
- Leverage external control data via frequentist or Bayesian methods during analysis to increase power
- Consider interim assessment of similarity between concurrent control patients and external control patients
 - If highly similar, randomization could cease
 - If highly dissimilar, could revert to 1:1 randomization
- External data can be up- or down-weighted in analysis, with use of Bayesian methods

Nested Trial Design

- Two subgroups defined once microbiology results are available:
 - Patients infected with pathogens susceptible to control drug
 - Patients infected with pathogens resistant to control drug
- Statistical testing strategy:
 - Test for non-inferiority in susceptible group
 - Test for superiority in resistant group
- Conditional on positive results for the NI test, no adjustment for multiplicity is required for the superiority test
- Power is reduced for the superiority test but can be compensated for by conducting the NI test with high power
- Group sequential methods can be incorporated to ensure sufficient sample size for the resistant group

*Huque, et al. *Statistics in Medicine* (2014)

Cluster Randomization

- Trial network can facilitate use of cluster randomization
 - Treatments randomly assigned to clinics, rather than patients
 - Primary motivation is to facilitate enrollment
 - Study participation may be more attractive to some patients
 - Acceleration of study treatment may reduce need for prior therapy
 - Ideally have a large number of clinics and small number of patients per clinic, e.g., resistant pathogen trial
 - Efficiencies within clinics in training and trial conduct similar to those realized with single-arm studies
 - More common in research studies than regulatory studies, but may have a place in anti-bacterial development

Cluster Randomization

- Statistical considerations
 - Impact on sample size, e.g., with a cluster size of 5 and intra-class correlation coefficient of 0.01, design effect = 1.04 → 4% sample size increase for same power
 - Statistical analysis more complicated to account for clustering of patients; degrees of freedom = # clusters and not # patients
 - Trade-off in potential sample size gain due to higher enrollment versus loss due to clustering

Leveraging of Control Subjects

- Use of common protocol with standard procedures, visit schedules, and CRFs allows control patients to contribute data to both trials
- Network should include a 'neutral 3rd party' (e.g., CRO or academic coordinating center) to manage data collected at clinics and retrieved from central labs and to conduct data analysis
- Logistical considerations are not trivial
- Issues of unmasking treatment assignments for one study, while another is ongoing, and some control patients are shared between the two, need to be addressed up front

Leveraging of Control Subjects

- Example:
 - Drug A's trial is actively recruiting with 1:1 randomization allocation of Drug A vs. standard of care (SoC)
 - Drug B's trial is approved to begin recruitment in same study population
 - Randomization of eligible patients changes at this point to 1:1:1 corresponding to Drug A: Drug B: SoC
 - If enrollment is completed for Drug A's trial, while Drug B's trial is still ongoing, then
 - Randomization allocation reverts to 1:1 for Drug B: SoC
 - Control patients in Drug A's trial have their data unmasked for analysis of the Drug A protocol but remain masked in Drug B's trial

Leveraging of Control Subjects

- Essential to this process is a CRO/Coordinating Center able to establish appropriate firewall procedures to maintain masking of patients among the various trials
- Sharing control patients does not imply that comparisons among active drugs are carried out
- Trial close-out for one protocol while the other is ongoing, and some control patients are shared, will impact operations at the clinics
- *Assuming logistical considerations can be addressed*, the benefit to sharing control patients could be substantial in terms of both recruitment time and trial costs

Multiple Infection Sites

- Enroll patients with related infection types in a single trial, using stratified randomization
- Hypothetical example: Mortality endpoint; resistant pathogens; superiority trial

Infection types	Standard of Care	Test Drug	Difference (95% CI)
Blood stream	15/30 (50.0)	5/30 (16.7)	30.3 (9.8, 53.7)
Intra-abdominal	7/15 (46.7)	3/15 (20.0)	26.7 (-7.2, 55.4)
HAP	7/15 (46.7)	10/15 (66.7)	-20.0 (-50.7, 51.7)
Pooled	29/60 (48.3)	18/60 (30.0)	18.3 (0.9, 34.8)

*Example generated for CTTI Statistics Think Tank Aug. 2012

Multiple Infection Sites

- Simple pooling of results across body sites can support a broader indication
 - If clinically meaningful to pool, considering disease severity and dose
 - Infection types are patho-physiologically similar
 - If there is some evidence of consistency of results and replication across body sites
 - Multiplicity issues arise if claim is sought for only those indications showing positive results
- In example, HAP results inconsistent with other sites

Multiple Infection Sites

- Alternative approach based on modeling that accounts for heterogeneity across infection sites
- Bayesian hierarchical modeling
 - Assume subgroups are exchangeable in the hierarchical model
 - Covariate adjustment may be needed for exchangeability
 - Test for overall treatment effect (does the drug work?) supplemented by subgroup estimates that are ‘smoothed’ under the model
 - Clustering can separate infection sites with positive results versus sites with less favorable results

Summary

- Anti-bacterial clinical trials are challenging
- Trial networks with established infrastructure and use of a common protocol can address many of the challenges
 - Optimize trial design and conduct to realize efficiencies and improve data quality through centralization of processes, systems, and training
- Innovative trial designs could be considered, given the network infrastructure and resources available to implement such designs
- Overall objective is to reduce time and cost of developing promising anti-bacterial drugs

References

- Antibacterial Drug Development Project. Clinical Trials Transformation Initiative website.
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- Huque MF, Valappil T, Song G. Hierarchical nested trial design (HNTD) for demonstrating treatment efficacy of new antibacterial drugs in patient populations with emerging bacterial resistance (2014) *Statistics in Medicine*
- Gamalo MA, Tiwari RC, LaVange LM. Bayesian approach to the design and analysis of non-inferiority trials for anti-infective products (2013) *Pharm Stat.*
- Dane A and Wetherington JD. Statistical considerations associated with a comprehensive regulatory framework to address the unmet need for new antibacterial therapies (2014) *Pharm Stat.*
- Viele K, Berry S, Neuenschwander B, et al. Use of historical control data for assessing treatment effects in clinical trials (2013) *Pharm. Stat.*

Success!

- A successful outcome for the day will
 - Be a lively exchange of ideas from varied statistical perspectives (academic, industry, and regulatory)
 - Generate proposals for innovative study design and analysis that FDA statisticians can pursue for regulatory feasibility
 - Prompt continued discussion among participants post-meeting on research ideas of mutual interest
- Thank you for your willingness to participate and engage!

** Slide is borrowed from CTTI Think Tank 2012

Framework for Morning Session

- **Focus of morning session:** Update on the current status of antibacterial drug development and ongoing challenges in the design and analysis of antibacterial drug products
- Four presentations will assist in framing the discussion
 - Summary of Regulatory Standards and Guidances
 - Summary of Unmet Need Pathway and Statistical Challenges
 - Application of PK/PD in Anti-Infective Drug Development
 - Statistical Considerations for a Tiered Approach
- Questions and Answers on Presentations

Questions to Guide Discussion

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