

COMBACTE STAT-Net

Improving the design and feasibility of clinical trials for new antibacterial agents

INTRODUCTION

Improving the design and feasibility of randomised clinical trials (RCT) for new antibacterial agents is key to promote the research and development of such needed new drugs^{1,2}. Simplifying the design of antibacterial RCT is the focus of several initiatives and public-private collaborations including the CTTI³, the FNIH⁴ and COMBACTE-Net WP4 – STAT-Net⁵. As one of the networks in the IMI's New Drug for Bad Bugs (ND4BB) program⁶, STAT-Net is a network of academic and EFPIA partners with specific expertise in PK/PD, modelling, biostatistics, infectious diseases, antimicrobial agents, microbiology, epidemiology and clinical development.

OVERALL OBJECTIVE

To support the clinical development of new antibacterial drugs by investigating approaches to improve the data-driven design of Phase 2 and 3 RCT.

OBJECTIVE 1: STAT-Net survey

University of Geneva; S Harbarth, E Bettli
AstraZeneca: D Wilson

GlaxoSmithKline; T Ashton

Conduct a survey to identify and prioritize the most important hurdles in clinical development for new antibacterials, with a focus on multidrug resistant organisms (MDRO) and trial design issues. Published in Antimicrob Agents Chemother. 2015 Jul;59(7):3695-9.

OBJECTIVE 2: Perform advanced biostatistical and PK/PD modelling

North Bristol NHS Trust; A MacGowan, A Lovering

Erasmus Medical Center; J Mouton, F de Velde
AstraZeneca; D Wilson

GlaxoSmithKline; T Ashton

- Assess the evidence supporting the linkage between pre clinical PK/PD predictions and the observed clinical efficacy and emergence of resistance to support the stronger use of PK/PD modelling in clinical trial design and future drug development and approval.
- Develop and evaluate sophisticated PK population models from phase 1 studies to better support Phase 2 or 3 dose-confirmation or efficacy trials as well as integrate PK data from phase 2 and 3 studies in overall trial evaluation.
- Explore (A) clinical exposure response relationships and issues in trial design, data capture and analysis and (B) pre-clinical aspects of oral administration and β -lactam- β -lactamase inhibitor interactions using amoxicillin-clavulanate as an example.



OBJECTIVE 3: Evaluate novel RCT design strategies based on modern biostatistical and epidemiological concepts to increase efficiency and success rates of trials.

University Medical Center Utrecht; R Eijkemans, S Nikolakopoulos

- Evaluate the methodological challenges associated with cluster randomized trial designs and the adaptive master trial protocol design.

- Consider alternative approaches for designing and analysing clinical development programs for broad and narrow spectrum antibacterial drugs active against MDRO.

- Assess methodology required for trial designs for broad- versus narrow-spectrum antibiotics, including non-inferiority and superiority to be tested in the same trial, and also diagnostics as part of the design of a trial.

University of Zurich; L Held, I Gravestock

Use Bayesian methods to model how accumulating data might indicate and predict the final clinical outcome to assess the ability to use Bayesian methods to shape the clinical development program of new antibiotics. More specifically:

- Consider how Bayesian methods such as hierarchical models, power priors and meta-analytic techniques can be used to augment the design and analysis of clinical trials for anti-infectives with co-data.
- Investigate the application of Bayesian methods in enhancing the precision of estimates from paediatric trials based on the design and/or data from adult trials.
- Investigate the use of estimates from one body site of infection to improve precision in alternative body sites.

Medical Center – University of Freiburg; M Schumacher, M Wolkewitz, H Sommer
University of Ulm; J Beyersmann

Plan and provide more informative analyses of complex time-to-event patterns that can occur in randomized controlled trials of antimicrobial drugs, by adopting a simulation-based approach. Special analytical consideration will be given to issues

related to confounding that can occur over time (after randomization), missing data and competing event problems.

Inserm/Paris Diderot University/Hopital Bichat; J-F Timsit, E Weiss, JR Zahar

Improve the accuracy of endpoints in trials of severe infectious diseases. Assess the inclusion criteria of previous randomized controlled trials of antibiotics against MDRO to identify if they have been driven by clinical criteria rather than designed to focus on specific patient populations and MDRO

2015 NEWS

In 2015, 10 abstracts from STAT-net partners were presented either orally or by poster at international conferences in Europe and the US.

Several manuscripts have been submitted or are in the final stage of preparation.

To capitalize on STAT-Net expertise and thanks to its network structure, STAT-Net partners are actively involved in several other ND4BB projects which kicked-off in 2015 (COMBACTE-MAGNET, COMBACTE-CARE, DRIVE-AB).

Four STAT-Net partners had the chance to discuss informally with EMA's Infectious Diseases Working Party (IDWP) their research on new statistical methodologies and left the meeting with very useful and constructive feedback and homework.

Two partners participated to the EMA workshop on revising the PK/PD guidance.

CONTACT INFORMATION:

STAT-Net program management office:

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EFPIA lead: D Wilson, AstraZeneca

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References

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2. Nambiar S, Laessig K, et al. 2014. Clin Pharmacol Ther 96:147-149.
3. Talbot GH, Powers JH, et al. 2012. Clin Infect Dis 55:1114-1121.
4. COMBACTE-Net. Combating bacterial resistance in Europe. <https://www.combacte.com/>.
5. Clinical Trials Transformation Initiative (CTTI) Antibacterial drug development projects. <http://www.ctti-clinicaltrials.org/what-we-do/ctti-project-categories/antibacterial-drug-development>.
6. ND4BB. New Drugs for Bad Bugs. <http://www.imi.europa.eu/content/nd4bb>

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