ND4BB COMBACTE

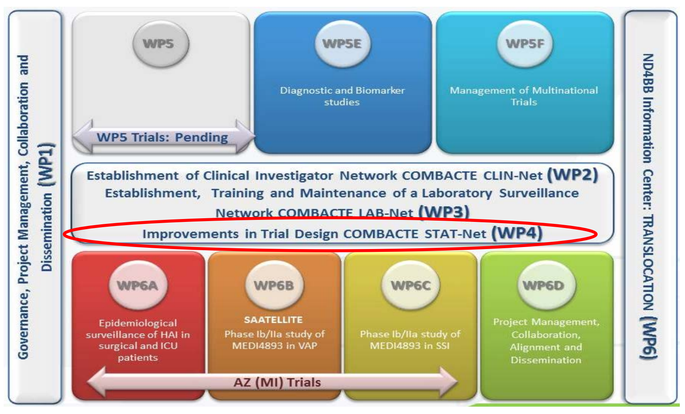
COMBATTING BACTERIAL RESISTANCE IN EUROPE

COMBACTE STAT-NET

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

INTRODUCTION

To improve the design and feasibility of clinical trials for new antibacterial agents is key to promote the research and development of such needed new drugs[1,2].
Simplifying the design of antibacterial clinical trials is the focus of several initiatives and public-private collaborations including the Clinical Trials Transformation Initiative (CTTI)[3], the Foundation for the National Institute of Health (FNIH)[4] and COMBACTE WP4 – STAT-Net[5]. As one of the networks in the Innovative Medicine Initiative (IMI)'s New Drug for Bad Bugs (ND4BB) program[6], 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.



MAIN OBJECTIVE

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

OBJECTIVE 1: STAT-NET Survey

University of Geneva; Stephan Harbarth, Esther Bettiol

AstraZeneca: David Wilson

GlaxoSmithKline; Theresa 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. A poster of the survey results was presented at ECCMID 2014 and a manuscript is currently in press.

OBJECTIVE 2: Perform advanced biostatistical and PK/PD modelling

North Bristol NHS Trust; Alasdair MacGowan, Andrew Lovering
Erasmus Medical Center; Johan Mouton, Femke de Velde
AstraZeneca; David Wilson
GlaxoSmithKline; Theresa 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 βlactam-βlactamase inhibitor interactions using amoxicillin-clavulanate as an example.

References

1.Bax R, Green S. 2015. J Antimicrob Chemother 2015 Jan 28 [Epub ahead of print].

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. 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/ab-drug-development.

6.ND4BB. New Drugs for Bad Bugs. http://www.imi.europa.eu/content/nd4bb

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

• ***University Medical Center Utrecht; Kit Roes, Esther Oomen, Stavros 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; Leonard Held, Isaac 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; Martin Schumacher, Martin Wolkewitz, Harriet Sommer***
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 randomisation), missing data and competing event problems.

• ***Inserm / Paris Diderot University / Hopital Bichat; Jean-Francois Timsit***
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

• ***University of Ulm; Jan Beyersmann***

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Unique in its scale, ambition, and its potential benefits for patients, public health and pharmaceutical research in Europe, COMBACTE has the potential to become the powerhouse of anti microbial drug development in Europe that could serve as a standard for other groups. Join us!

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