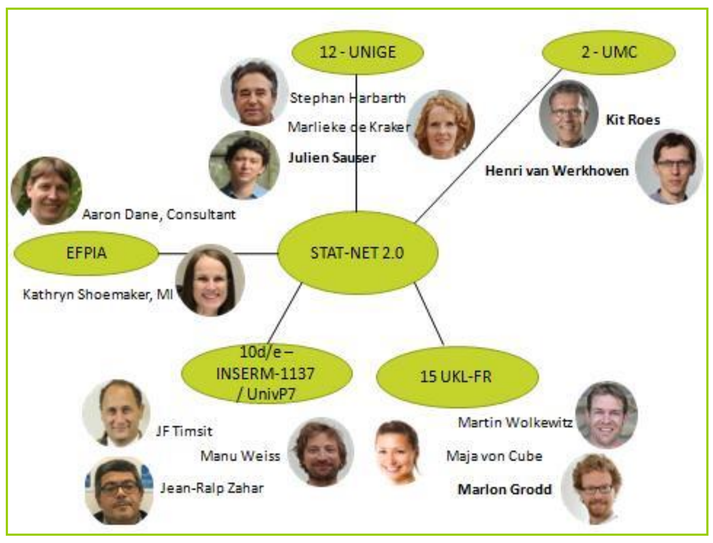
COMBACTE-NET
STAT-Net 2.0 2018-2021

Optimising the design and analysis of clinical trials for antibiotics against multidrug-resistant organisms

INTRODUCTION

There is a wide gap between the number of new antibacterials in research and development (R&D) and the medical need caused by the increasing prevalence of infections by multidrug-resistant organisms (MDROs). Innovative trial designs and analytical methods could be an important tool to promote R&D efforts for new antibacterials. After a first, successful funding period (2013-2017), STAT-Net will continue their efforts to improve clinical trial validity and efficacy and thus contribute to efficient market approval of effective antibacterials.



OVERALL OBJECTIVE

Apply expertise of STAT-Net to further ongoing and future RCTs for antibacterial development within COMBACTE, focusing on three pillars:

1. **Reappraise engagement with regulatory agencies about novel trial designs, analysis techniques, clinical outcome definitions**
2. **Provide methodological and analytical input for an innovative adaptive platform trial**
3. **Provide epidemiological and statistical expertise to COMBACTE-NET partners as requested**

OBJECTIVE 1: REAPPRAISE ENGAGEMENT WITH REGULATORY AGENCIES

Medical Center – University of Freiburg; M Wolkewitz, M Grodd
Inserm/Paris Diderot University/Hopital Bichat; JF Timsit, E Weiss

- Engage with the regulatory agencies to provide a framework for the use of estimands in a competing risk setting
- In consultation with regulatory agencies, validate composite endpoints for hospital acquired and ventilator associated pneumonia (HAP/VAP) in a step-wise approach (1) Use OUTCOMEREA surveillance database (2) Use data from COMBACTE partners (prospective observational studies, EPI-Net) (3) Perform statistical simulations to support the validation of the composite endpoints.

OBJECTIVE 2: INNOVATIVE ADAPTIVE PLATFORM TRIAL

University of Geneva; J Sauser, M de Kraker
University Medical Center Utrecht; H van Werkhoven

- Assess the feasibility of a highly innovative adaptive platform trial to study multiple interventions in a single intervention in a perpetual manner in HAP/VAP patients. This will be done initially by setting up an observational study in ICUs in Eastern Europe.
- Identify the challenges related to the writing of a master protocol
- Evaluate the implementation of various adaptive designs and the possibility to combine multiple adaptions in the setting of a platform trial.
- Assess the statistical and operational hurdles related to such methods.
- Perform simulations to identify the most relevant designs and attempt to quantify the complexity of implementing adaptations.
- Explore the applicability of the novel statistical joint modeling methods to simultaneously analyse longitudinal and time-to-event data to increase clinical trial efficiency and achieve better estimations

OBJECTIVE 3: EPIDEMIOLOGICAL AND STATISTICAL CONSULTANCY

All partners

- MedImmune EVADE trial (MEDI3902; WP4). Improve feasibility of Ph II RCT
- DaVolterra ANTICIPATE trial (DAV132; WP7). Phase III trial; design, population, SAP
- Janssen ExPec10v (WP10). Study design
- Magnet EURECA/EPI-Net. Study design, SAP, analysis. Scientific input for AMR communication.

LATEST UPDATES

STAT-Net partners continue to present their results at conferences and publish manuscripts. Below the latest results:

1. Gravestock I, Held L. Power priors based on multiple historical studies for binary outcomes. *Biometrical Journal* 2018 *In press.*
2. Sommer H, Timsit JF, Von Cube M, et al. The Impact of Early Adequate Treatment on Extubation and Discharge Alive of Patients With Pseudomonas aeruginosa-Related Ventilator-Associated Pneumonia. *Critical Care Medicine* 2018; 46; 1643–1648.
3. Von Cube MK, Timsit JF, Sommer H. et al. Relative risk and population-attributable fraction of ICU death caused by susceptible and resistant Pseudomonas aeruginosa VAP: a competing risks approach. *Intensive Care Medicine* 2018; 44: 1177–1179.
4. De Kraker M, Sommer H, De Velde F, et al. Optimizing the Design and Analysis of Clinical Trials for Antibacterials Against Multidrug-resistant Organisms: A White Paper From COMBACTE's STAT-Net, *Clinical Infectious Diseases* 2018; 67: 1922–1931.
5. Weiss E, Zahar JR, Alder J, et al. Elaboration of consensus clinical endpoints to evaluate antimicrobial treatment efficacy in future HABP/VABP clinical trials. *Clinical Infectious Diseases* 2019 *In press*.

CONTACT INFORMATION

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