MEDICAL UNIVERSITY OF VIENNA

European Research Projects on Statistical Methodology to Enhance Clinical Trial Designs and Analysis

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EU Call in 2013

New methodologies for clinical trials for small population groups

FP7-HEALTH-2013-INNOVATION-1.

Objective

develop **new or improved statistical design methodologies** for clinical trials aiming at the efficient assessment of the safety and/or efficacy of a treatment for small population **groups in particular for rare diseases or personalised (stratified or individualised) medicine**.

Expected Impact

- **Cost efficient clinical trials deriving reliable results** from trials in small population groups.

3 EU Projects to enhance statistical methodology in SMALL POPULATIONS

MEDICAL UNIVERSITY OF VIENNA

asterix

Advances in Small Trials dEsign for Regulatory Innovation and eXcellence)

Coordinator: Kit Roes
FP7 HEALTH 2013 - 602144
http://www.asterix-fp7.eu/

InSPiRe
Innovative methodology for small populations research

Coordinator: Nigel Stallard
FP7 HEALTH 2013 - 603160
www.warwick.ac.uk/InSPiRe

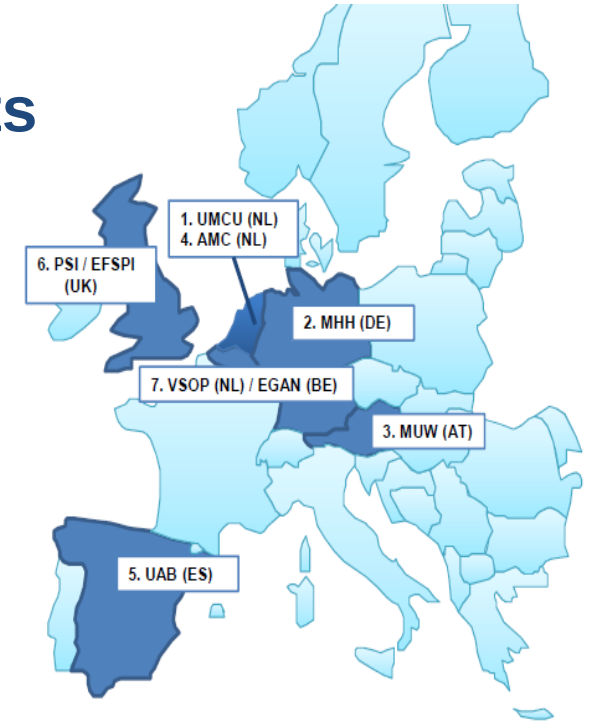
IDeAL

Integrated DEsign and AnaLysis of small population group trials

Coordinator: Ralf-Dieter Hilgers
FP7 HEALTH 2013 - 602552
http://www.ideal.rwth-aachen.de/

Concept and objectives of asterix

- Unmet need for drugs to treat rare diseases.
- Difficulty to establish efficient and reliable evidence from **clinical trials in small populations.**
- Absence of methods to include **patients and patient perspectives** to generate results that matter to patients.
- Uncertainty in **regulatory decision making** on new treatments.



WP2: New and improved methods for individual trial design

- assess currently used methods
- develop new novel trial designs and analysis methods
- focus on optimization strategies for individual trials

Especially, WP2 will focus on:

- recommendations for optimal randomisation strategies
- new methodology to integrate evidence from multiple endpoints for regulatory decision making
- improved sequential and adaptive designs using data from multiple endpoints
- Validity of adaptive designs in small populations
- adapted standards of evidence on a clinical trial level

Other WPs in Asterix:

WP3: New methods for prospective design and analysis of series of studies
WP4: Improved use of patient level information and perspectives
WP5: Validation of new methods within clinical as well as regulatory settings

Partners

UMC Utrecht	Kit Roes, Biostats / CBG (Coordinator)
AMC	Hanneke van der Lee, Epidemiology
Med Univ Wien	Martin Posch, Biostats / EMA
Hannover Med School	Armin Koch, Biostats / EMA
Un A de Barcelona	Ferran Torres, Biostats / EMA Carida Pontes
VSOP / EGAN	Cor Oosterwijk, Tessa vd Valk
PSI/EFSPI	Egbert Biesheuvel Federation of statisticians in industry

InSPiRe
Innovative methodology for small populations research

Project work packages

Work package 1: Research in early dose-finding trials in small populations

Work package 2: Research in decision-theoretic designs for clinical trials in small populations

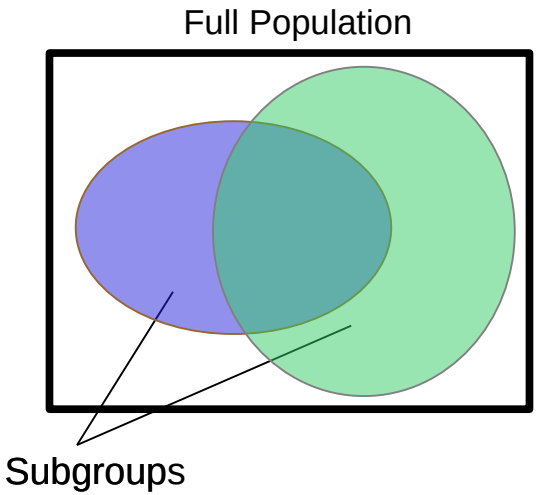
Work package 3: Research in confirmatory trials for small populations and personalized medicines

Objectives:
- to develop frequentist and decision-theoretic methods for identification and confirmation of subgroups with + benefit-risk balance
- to develop optimized adaptive enrichment designs

Work package 4: Research in the use of evidence synthesis in the planning and interpretation of clinical trials in small populations

Two Trials: Learn and Confirm

Learning (Phase II)

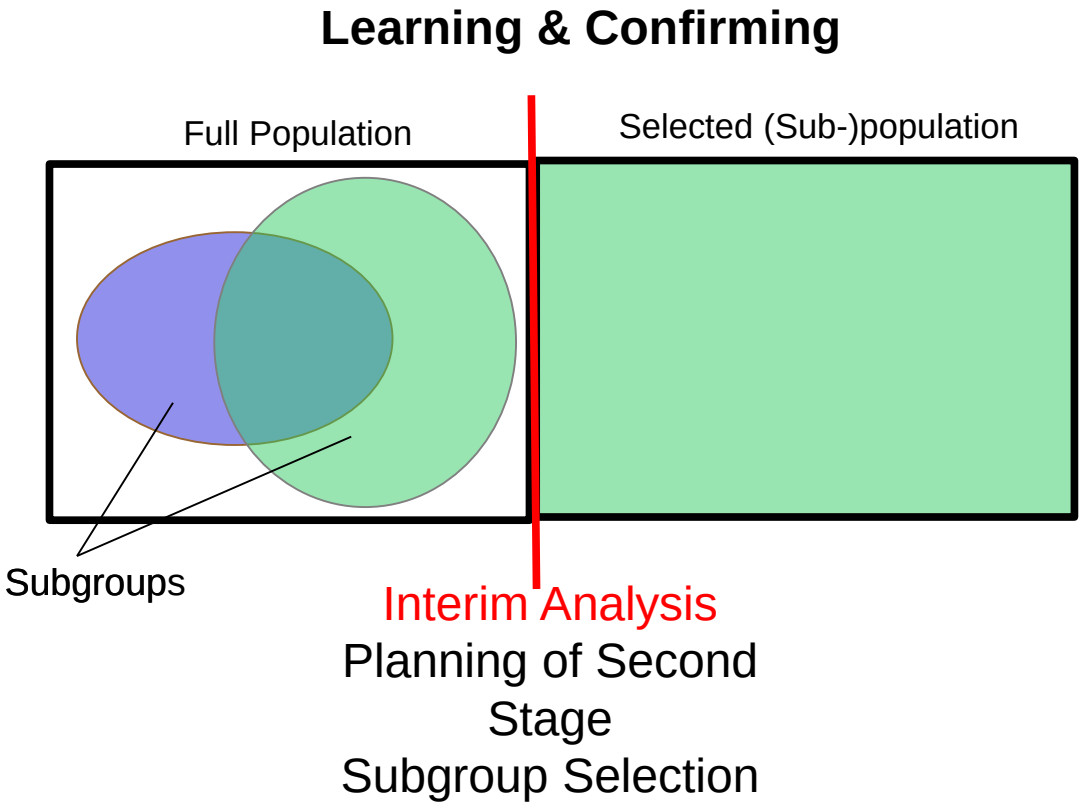


Planning Phase III
Subgroup
Selection

Confirming (Phase III)

- Phase II trial objective: subgroup identification
- Efficacy shown ONLY based on Phase III data (independent replication in the target (sub-)population).

Adaptive Enrichment Design



- First stage data is used for subgroup selection
- Efficacy is demonstrated with data from both stages (adjusting for multiplicity).

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Approaches Based on Utility Functions

- Define utility functions quantifying the loss and gains (false positive/false negative) of decisions on the efficacy of a treatment in different subgroups
- Utility functions for the perspectives of different stakeholders.
- Derive optimized selection rules that maximize the expected utility

Project partners
Coordinator Nigel Stallard

- The University of Warwick, United Kingdom
- Universitaetsmedizin Goettingen (UMG), Germany
- Medizinische Universitaet Wien (MUW), Austria
- Institut National de la Sante et de la Recherche Medical (INSERM), France
- Bundesinstitut fur Arzneimittel und Medizinprodukte (BfArM), Germany
- Stockholms Universitet, Sweden
- Quintiles Ltd, United Kingdom
- Clinical Trials Consulting and Training Ltd (CTCT), UK

IDEAL Work Packages and PIs

Assessment of randomisation procedures and randomisation based test in small population groups	**Ralf-Dieter Hilgers (project lead of IDEAL)** RWTH Aachen, Germany
Extrapolating dose response information to small population groups	**Holger Dette** Ruhr Universität Bochum, Germany
Adaptive design studies in small population groups	**Franz König** Medical University of Vienna, Austria
Optimal design in mixed models to analyse studies in small population groups	**France Mentré** INSERM, France
Design of pharmacogenetic small population groups trials including, crossover trials, n-of-1 trials and enrichment trials	**Stephen Senn** CRP SANTÉ, Luxembourg
Simulation of clinical trials in small population groups	**Mats Karlsson** Uppsala University, Sweden
Genetic factors influencing the response to the therapy in small population group trials	**Malgorzata Bogdan** POLITECHNIKA WROCŁAWSKA,Poland
Decision analysis in small population groups	**Carl-Fredrik Burman** Chalmers Univeristy, Sweden
Biomarker surrogate endpoints in small population groups	**Geert Molenberghs** Universiteit Hasselt & KU Leuven, Belgium
Dissemination of results	**Christoph Male (pediatrician, PDCO member)** Medical University of Vienna, Austria

Three main tasks in WP Adaptive Designs

- Task 1: Development of evidence levels for small population groups
- Task 2: AD for confirmatory model based decisions
- Task 3: AD to enable comparative effectiveness

T1: Development of evidence levels for SPGs

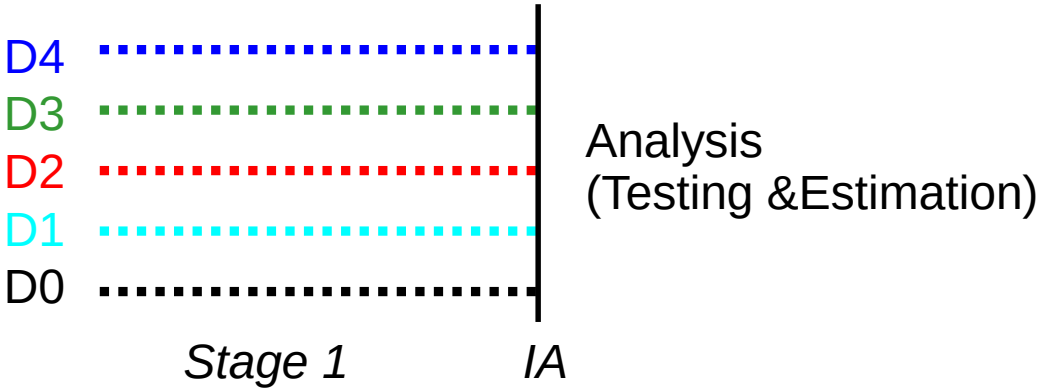
- Full development programme not feasible
- Use prior knowledge for inference in SPGs
- Studies conducted in related (larger) populations and/or similar drug substances basis for (partly) extrapolating efficacy and safety
- Depending on similarity →
  - adapt either the required level of evidence, sample sizes and/or testing strategy for SPGs
- Link between Bayesian methods and classical frequentist decision making criteria

T2: AD for confirmatory model based decision

- Adaptive clinical trials …
  - to perform efficient dose finding at an adaptive interim analysis (IA)
  - to confirmatory demonstrate efficacy using all accumulated data (before and after the IA)

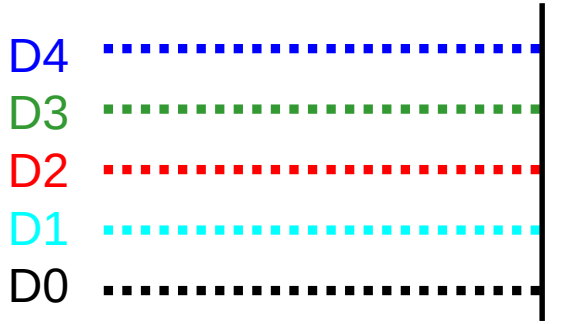
- Final decision based on
  - Clinically relevant endpoint
  - And/or appropriate surrogate parameters

Fixed Sample Design



Analysis
(Testing &Estimation)

Fixed Sample Design



Dose finding / PoC

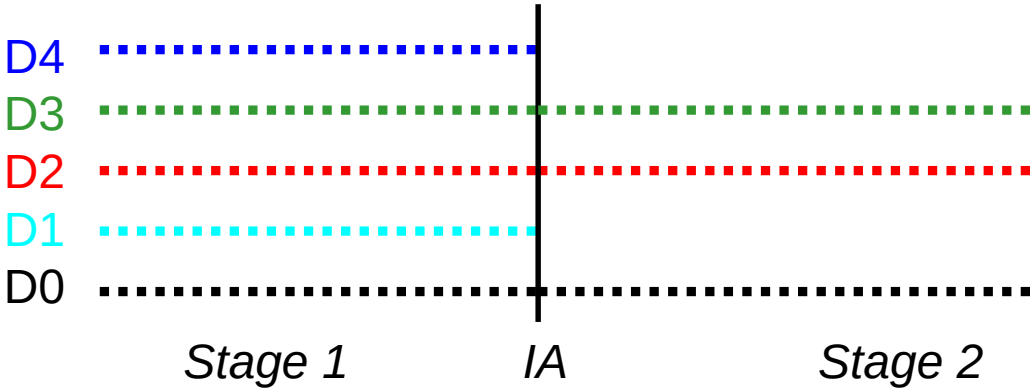
IA

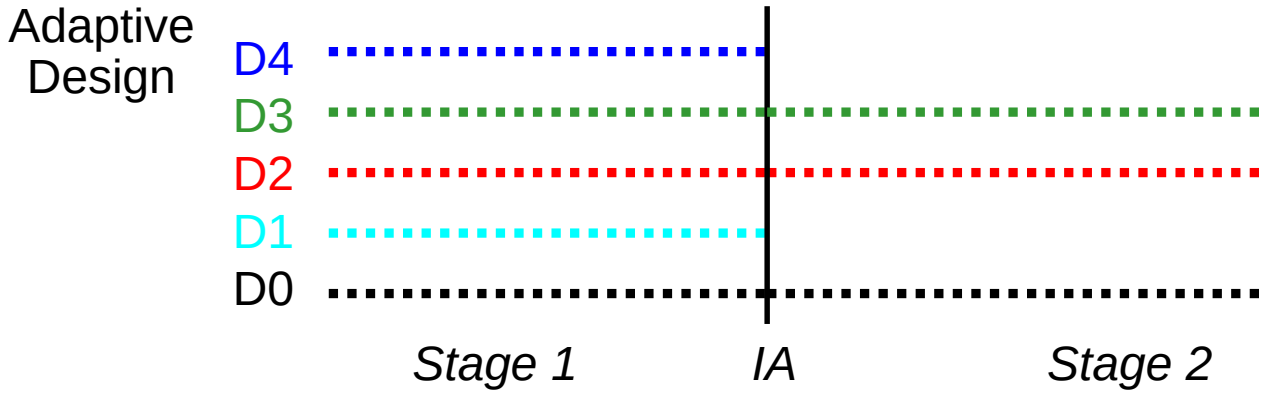
Based on results

Conduct a new study

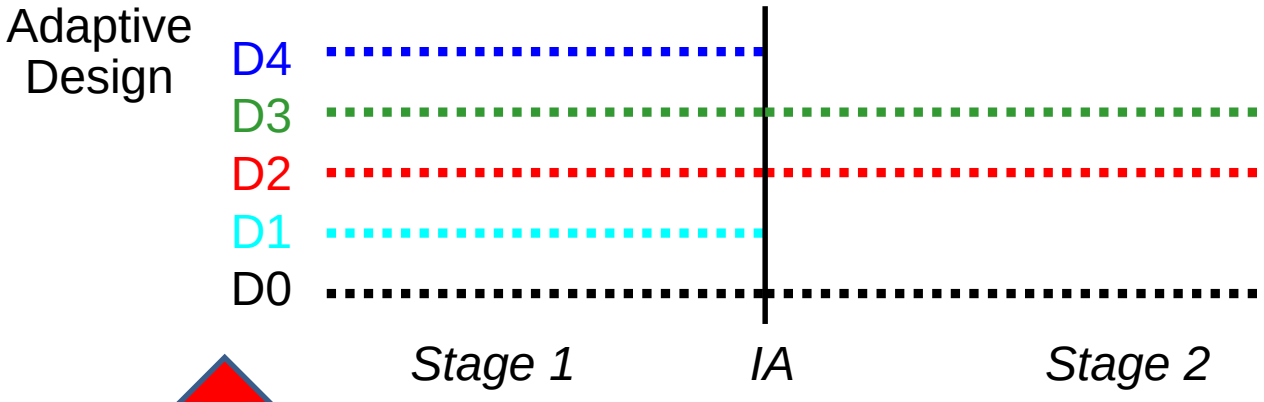
Pivotal study

Adaptive Design



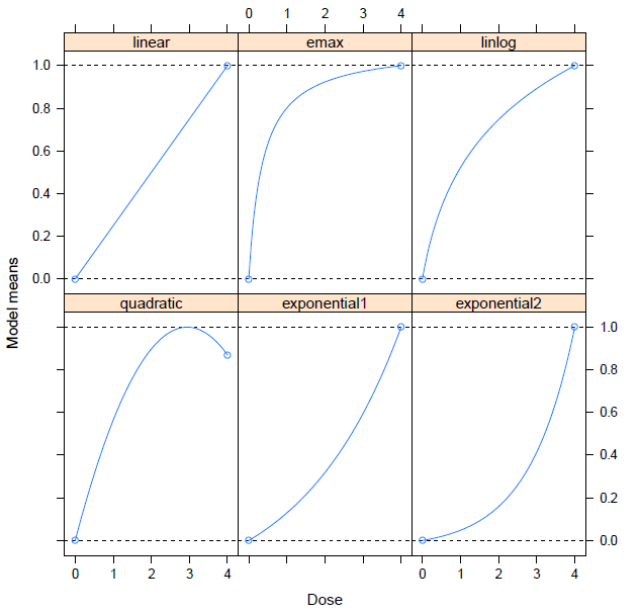


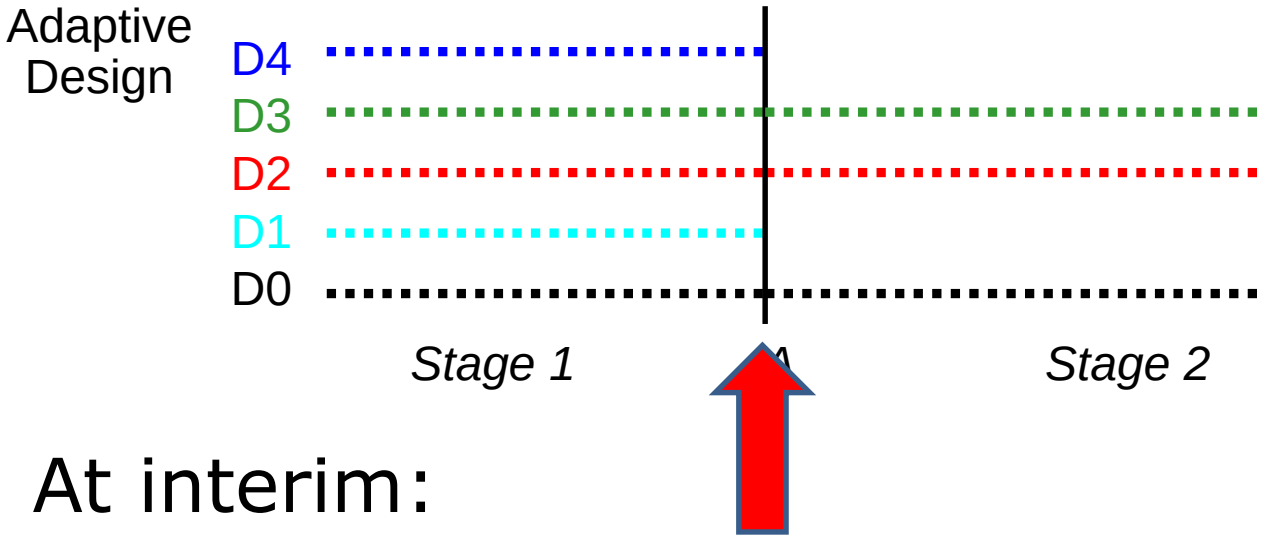
- We would like to use testing & modeling
- But how to deal with uncertainity concering specifying the right model?
- MCPMod (Bretz et al. 2004, Bretz et al. 2008, Bjornkamp et al. 2009)



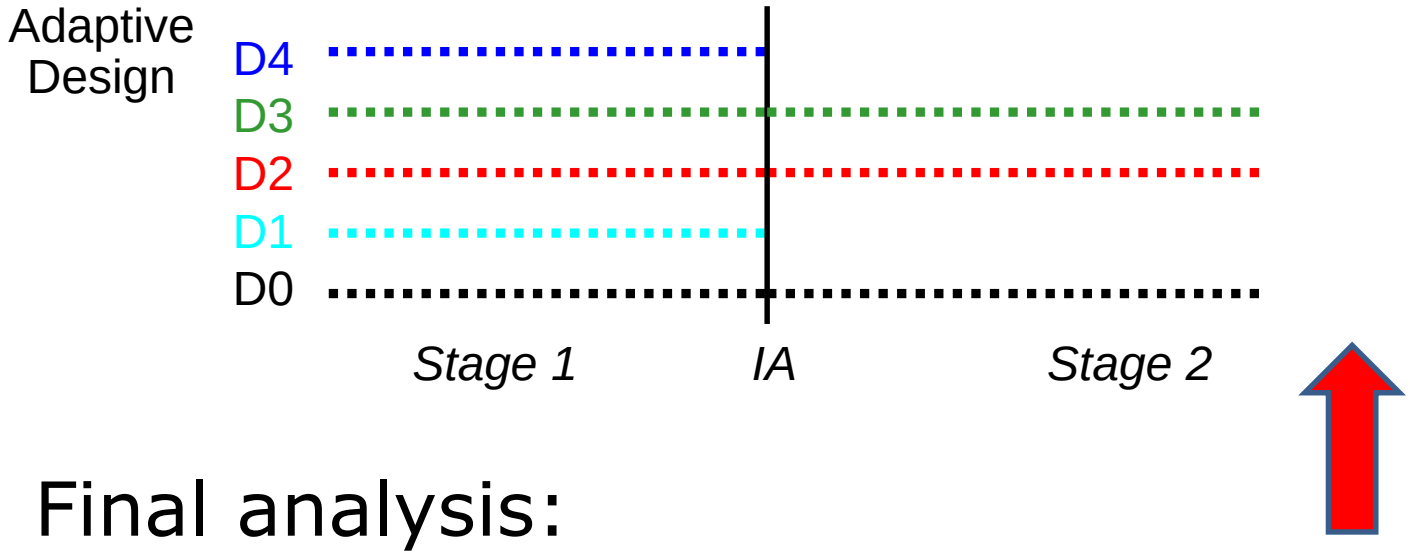
Before trial starts:

- Fix the design of the first stage (sample sizes, doses groups, ...)
- and candidate models for the first stage.





- At interim:
  - Fix the design of the second stage (adapt sample sizes, selection of doses, ...) and candidate models (drop/add models,refine parameter guesses).
  - Use the modeling part of MCPMod to support interim decisions (e.g., estimate MED or highest dose in a range ...)



- Final analysis:
  - Test PoC and/or elementary null hypotheses (for a single dose) using data from stage I + II with stage-wise trend tests.
  - Combine MCPMod, Adaptive Combination Tests and Closed Testing Principle to achieve type I error control

T3: AD to enable comparative effectiveness analysis

- How to address the different needs of regulators and reimbursers?
- Gold-standard: three arm trials (**E**xperimental, **P**lacebo, **A**ctive Comparator)
- Which available sample sizes allow which designs?

- Two-stage AD to drop or reduce sample size of placebo
- Response AD (with WP2): shift emphasis from **E-P** to the comparison **E-A** if evidence of efficacy of N becomes more and more promising

Improving Design, Evaluation and Analysis of early drug development Studies

IDEAS
Improving drug development

http://www.ideas-etn.eu/

IDEAS is a European training network for early stage researchers working on statistical methods for early drug development. The network is funded by the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 633567 and comprises of 8 full partners and three associated partners at major European universities, the pharmaceutical industry, and consulting companies. The project, which is coordinated by Lancaster University, started on 1. January 2015 and will run for 4 years.

- European training network
- 14 PhD students in medical statistics
- In addition to local requirements for PhD
- specific training on statistical methods for early drug development
- generic skills
- different stakeholders
- advisory board
- mobility program
- Long term goal: develop joint EU PhD curriculum for statisticians in early drug development

1. Dose finding for combination trials with many treatments read more...

2. Pooling information on progression-free and overall survival in multi-arm cancer trials read more...

3. Using pre-clinical information to establish a safe dose in first-in-men studies read more...

4. Development of a biomarker score to identify a subgroup of treatment responders read more...

5. The impact of data and safety monitoring board decisions to drop treatments read more...

6. Optimal designs and analysis methods for the development of Biosimilars read more...

7. Predictive probability of success, as a criterion at clinical development milestones read more...

8. Innovative designs for combination of existing therapies read more...

9. Modelling and simulation for the early development of a modified administration route read more...

10. Bias and precision in early phase adaptive studies and its consequences for the decisions about conducting and designing confirmatory studies read more...

11. Interval estimation for dose-finding studies read more...

12. Statistical methods for phase I/II trials of molecularly targeted agents in oncology read more...

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