IDEAL
Integrated Design and Analysis of small population group trials

DIA ADSWG Meeting 2014-02-28

Ralf-Dieter Hilgers
Carl-Fredrik Burman
Franz Koenig

http://www.ideal.rwth-aachen.de
Outlook

- SPG; why current drug development approaches are not addressing them appropriately

- Overview of the grant, consortium structure, 11 WPs

- Focus on two work packages:
  - Decision Analysis
  - Adaptive design

- Plans for collaboration with DIA ADSWG
The Problem

Rare disease
- European Community: 5 to 10000
- E.g. Gaumenspalte 50/100 000, CDG-Syndrom Typ Ij 1 case, Fine-Lubinsky-Syndrom 5 cases, Tietz-Syndrom 1 family

Subgroup Analysis
- Therapy Responder

Treatments
- Drugs
- Surgical procedures
- Medical Devices etc.

Orphanet, 2012
Embedding

- EURORDIS – The Voice of Rare Disease Patients in Europe
- National plans or strategies for rare diseases
- EU initiatives on rare diseases
- Orphanet (The portal for rare diseases)
- International Rare Diseases Research Consortium (IRDiRC) 2011
Orphan Drug Use in Rare Disease

- Transfer from animals to human
- Design
- Building computational models of a disease and simulate trial designs
- Outcomes – scores
- Long term survival
- Identify biomarker
- Mirror clinical pathways
- Extrapolation
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.
IDEAL Project (started on 1st Nov 2013)
## IDEAL Work Packages and PIs

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<th>PI</th>
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<tr>
<td>Assessment of randomisation procedures and randomisation based test in small population groups</td>
<td>Ralf-Dieter Hilgers (project lead of IDEAL)</td>
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<tr>
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<td>RWTH Aachen, Germany</td>
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<td>Extrapolating dose response information to small population groups</td>
<td>Holger Dette</td>
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<td>Ruhr Universität Bochum, Germany</td>
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<td>Adaptive design studies in small population groups</td>
<td>Franz König</td>
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<td>Medical University of Vienna, Austria</td>
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<td>Optimal design in mixed models to analyse studies in small population groups</td>
<td>France Mentré</td>
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<td>INSERM, France</td>
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<td>Design of pharmacogenetic small population groups trials including, crossover trials, n-of-1 trials and enrichment trials</td>
<td>Stephen Senn</td>
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<td>CRP SANTÉ, Luxembourg</td>
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<td>Simulation of clinical trials in small population groups</td>
<td>Mats Karlsson</td>
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<td>Uppsala University, Sweden</td>
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<td>Genetic factors influencing the response to the therapy in small population group trials</td>
<td>Malgorzata Bogdan</td>
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<td>POLITECHNIKA WROCŁAWSKA,Poland</td>
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<tr>
<td>Decision analysis in small population groups</td>
<td>Carl-Fredrik Burman</td>
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<td>Chalmers University, Sweden</td>
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<td>Biomarker surrogate endpoints in small population groups</td>
<td>Geert Molenberghs</td>
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<td>Universiteit Hasselt &amp; KU Leuven, Belgium</td>
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<td>Dissemination of results</td>
<td>Christoph Male (pediatrician, PDCO member)</td>
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<td>Medical University of Vienna, Austria</td>
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FP7 HEALTH 2013 - 602552
Workpackages
Management Structure
### External Scientific Advisory Board

#### Regulators, patient representatives, clinicians, statisticians, ...

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
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<tbody>
<tr>
<td>Dr. Jordi Llinares, Dr Ralf Herold</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>Dr. Gerard Nguyen</td>
<td>Rett Syndrome Europe, PDCO patient representative member (EURORDIS), Member of EUCERD,...</td>
</tr>
<tr>
<td>Dr. Odile Kremp</td>
<td>Director of Orphanet</td>
</tr>
<tr>
<td>Prof. Gerard Pons</td>
<td>PU-PH/CS chez Univ Paris Descartes APHPPU-PH/CS chez Univ Paris Descartes APHP</td>
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<tr>
<td>Prof. Tomasz Burzykowski</td>
<td>IDDII Inc., (International Drug Development Institute)</td>
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<tr>
<td>Dr. Paolo Baroldi</td>
<td>Vanda Pharmaceuticals Inc</td>
</tr>
<tr>
<td>Prof. Gernot Wassmer</td>
<td>AptivSolutions</td>
</tr>
<tr>
<td>Prof. Frank Bretz</td>
<td>Novartis Pharma</td>
</tr>
<tr>
<td>Prof. Rosemary Bailey</td>
<td>School of Mathematics and Statistics, University of St Andrews</td>
</tr>
<tr>
<td>Dr. Martin Forster</td>
<td>Department of Economics and Related Studies, University of York</td>
</tr>
<tr>
<td>Prof. Steven A. Julious</td>
<td>Medical Statistics Group, The University of Sheffield</td>
</tr>
<tr>
<td>Dr Paolo Pertile</td>
<td>Faculty of Economics, Verona University</td>
</tr>
<tr>
<td>Prof. William F. Rosenberger</td>
<td>Department of Statistics, George Mason University</td>
</tr>
<tr>
<td>Prof. Chiara Sabatti</td>
<td>Associate Professor of Health Research and Policy and of Statistics at Stanford</td>
</tr>
<tr>
<td>Prof. Günther Schmalzing</td>
<td>Department of Molecular Pharmacology, RWTH Aachen, Germany / Lead of Ethics Committee RWTH Aachen</td>
</tr>
<tr>
<td>Prof. Christopher Jennison</td>
<td>Department of Mathematical Sciences, University of Bath</td>
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</table>
Name: Assessment of randomisation procedures and randomisation based test in small population groups

Deliverables

2.1. Bias assessment of randomisation procedures

2.2. Development of adequate randomisation procedures for small population groups

2.3. Development of randomisation test for small population groups
Work Package 9
DECISION ANALYSIS IN SMALL POPULATION GROUPS

Work package leader:
Carl-Fredrik Burman
Chalmers University
Background

-The Decision Analysis (DA) work package is partly inspired by the work in the DIA ADSWG Adaptive Programme (AP) wks
  - Decision theoretic
  - Bayesian “in-house” + perhaps frequentist to costumer (foretelling stakeholder analysis)
  - Study optimisation
  - Programme optimisation
Objectives (following grant application)

- “... to improve the rational basis for decisions, and help align different stakeholder perspectives.”

(Method)

- A Bayesian decision theoretic framework will be applied, but the priors for efficacy and safety may be more or less conservative for different stakeholders.
- In addition, pure frequentist decision rules will be considered for e.g. regulatory agencies.”
Deliverables

- D9.1) Guidance regarding stakeholder decision rules: The deliverable will be a decision theoretic framework for the main decisions made by key stakeholders (patient, prescribing physician, HTAs, RAs) which will include an analysis of the impact of certain stakeholder decisions on the expected clinical utility in the population.

- D9.2) R code for the optimisation of confirmatory trials with respect to dose selection and sample size, given certain stakeholder decision rules (see D9.1).

- D9.3) Recommendations for how decisions on late stage trial design and treatment utilisation in small populations should be taken by relevant stakeholders, using the decision theoretic framework. This includes late stage investment decisions taken by pharmaceutical companies, as well as regulatory approvals and reimbursement decisions. (Hoping for: programme optimisation)
Example: RA + sponsor; focus on efficacy

- Limited (small) population size, N
- Test NEW drug vs CONTROL in n patients
- Possible regulatory rules
  - No regulatory hurdle
  - One trial $p<0.025$ (or e.g. $p<0.1$)
  - Two trials $p<0.025$

- What is optimal trial (/program) size, n?
  Based on prior.
  - Optimal meaning “best outcome among N pat’s” (societal perspective)
  - Optimal Net Present Value (commercial perspective)
  - Optimal for individual trial patient (ethical)
  - Adaptivity?
Variation: Include safety

- Estimated efficacy, \( E \)
- Estimated safety \( S \)
- Possible regulatory benefit/risk hurdles:
  - \( S < K \)  
    Estimated safety
  - \( S + 1.96 \text{SE}(S) < K' \)  
    Non-inferiority
  - \( E - c \cdot S > 0 \)  
    Estimated B/R
  - \( E - c \cdot S - 1.96 \text{SE}(E-c\cdot S) > 0 \)  
    Proven positive B/R
- How would you model the RA decision rule?

- Optimise trial design, given priors.
Variations: some extensions

- As before, but add
  - Payer hurdle: e.g. based on estimated cost-effectiveness
  - Patient heterogeneity, modelling efficacy and safety as functions of patient covariates
  - Dose choice for phase III
  - Potential of two doses in phase III
  - Simultaneous optimisation of programme design, including dose-response phase IIB and confirmatory phase III
  - Biomarker issue in study (/programme) design
AP potential model components

- Ph IIb
  - Go / No Go
  - Design

- Ph III
  - Go / No Go
  - Design

Prior information

Phase IIb

Phase III

Regulatory evaluation

Commercial

Benefit/risk (enters everywhere)

Project Prioritisation

Biomarker in ph IIb?

Dose Adaptation?

Two doses?

Seamless?

Adaptation?

Uncertain response (even given data)

 Depends on efficacy, safety, timing
New working group, within DIA ADSWG Adaptive Programmes

Co-chaired by Bob Beckman, Cong Chen

2nd TC a week ago

Preliminary initial focus on treatment-predictive biomarker

- Say that biomarker X is likely predicting treatment benefit (vs control)
- For which values of X will NEW be beneficial?
- How to design trial(s) to evaluate biomarker dependence and verify efficacy in a subpopulation?
All members of the Adaptive Programme core team (at that time) were mentioned in the grant application as supporting IDEAL

- New AP small population WG
- Membership overlap
- Volunteers for collaborations?
Organisation of WP9 Decision Analysis

- Led from Chalmers Univ, Sweden
- Collaboration with other universities
- Principal investigator: Carl-Fredrik Burman
- PhD student: Sebastian Jobjörnsson
- Senior researcher: Petter Mostad
- Ongoing collaborations
  - Martin Forster, Paolo Pertile (Health Economics)
  - DIA small population WG
Work Package 4
ADAPTIVE DESIGNS

Work package leader:
Franz Koenig
Medical University of Vienna, Austria
Medical University of Vienna – what? who?

- Medical University of Vienna (MUW)
- Center for Medical Statistics, Informatics, and Intelligent Systems (CEMSIIS)
- Section of Medical Statistics (IMS)

- Head (since 2012): Prof. Martin Posch
- Emeritus Prof. Peter Bauer
- Head of working group „Adaptive Designs“: Franz König
- See www.meduniwien.ac.at/medstat
Who is supposed to do the work in WP4?

**MUW Permanent staff:**
- Peter Bauer
- Franz König (PI IDEAL WP Adaptive)
- Florian Klinglmüller

**MUW – 2 IDEAL PhD students:**
- Gerald Hlavin
- Sergey Krasnozhon

**Two stays abroad planned:**
- Novartis, Basel (1 month)
- AptivSolution, Cologne (1 month)

**UKA, RUB, PWR, CTH, …**

… AND HOPEFULLY WE WILL COLLABORATE WITH DIA ADSWG AND ITS WGs
Classical Clinical Trials with pre-specified Design

Pre-specified Design Parameters:
- Sample Size
- Population
- Treatments (doses)
- Outcome variable(s)

- Dealing with the unexpected?
- Classical fixed trial paradigm allow little learning during the conduct of the trial.

Medical Statistician: one who will not accept that Columbus discovered America … because he said he was looking for India in the trial* plan. (* A cross over trial)  
Stephen Senn, 1997, p 58
“Fully” adaptive (flexible) designs

Adaptive or flexible designs allow for mid-trial design modifications based on information from in- and outside the trial without compromising on the false positive error rate (and hopefully improving the performance of the running trial).

To control the type I error, the design modifications need not be specified in advance!

Three main tasks in WP 4

- **Task 1**: Development of evidence levels for small population groups
  - Task Leader: MUW

- **Task 2**: AD for confirmatory model based decisions
  - Task Leader: MUW; Partner: RUB, PWR

- **Task 3**: AD to enable comparative effectiveness
  - Task Leader: MUW; Partner: UKA, CTH
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
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

Stage 1

IA

Analysis (Testing & Estimation)

D4
D3
D2
D1
D0
Fixed Sample Design

D4  D3  D2  D1  D0

Based on results
Conduct a new study

Dose finding / PoC  IA

Pivotal study
- We would like to use testing & modeling
- But how to deal with uncertainty concerning specifying the right model?
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 ...)

Adaptive Design

<table>
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<tr>
<th>Stage 1</th>
<th>Stage 2</th>
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<td>D3</td>
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<td>D1</td>
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<td>D0</td>
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- **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 (Experimental, Placebo, Active 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
What shall be delivered by IDEAL?
What shall be delivered by all IDEAL WPs?

- Papers in statistical journals
- Review papers
- Free software code (in R) & manual, e.g., to assess operating characteristics of proposed adaptive designs
- Shortcourses, e.g., on adaptive designs
- Online survey to assess status-quo in 2014:
  - involving all important stakeholders
- Regular meetings
  - Open symposium on small population, 1-2 July 2014, Vienna
  - Investigator meeting in November 2014, Paris

- Input to regulatory guidance documents (see next slide)
IDEAL sent comments to EMA on
- ‘Draft guideline on adjustment for baseline covariates’ (EMA/295050/2013)
- MCP-Mod as an efficient statistical methodology for model-based design and analysis of phase II dose finding studies under model uncertainty.

Next steps:
- Draft EMA Guideline on the investigation of subgroups in confirmatory clinical trials
- Reflection Paper on “Extrapolation of efficacy and safety in medicine development”
Plans for collaboration with DIA ADSWG
INTERACTION with DIA

- Link between DIA ADSWG and IDEAL
  - Carl-Fredrik (chair of DIA ADSWG AP and member in DIA ADSWG)
  - Franz (in ADSWG and DIA ADSWG and DIA Working Group „Small Populations“)

- Joint research projects

- Input to IDEAL Online-Survey
Symposium on Small Populations, 1-2 July

- Symposium on Small Populations
  1st and 2nd of July 2014
  Vienna, Austria

- Joint symposium of three FP7 projects on small populations

- Includes post-conference short courses on
  - Surrogate marker evaluation in clinical trials
  - Randomisation in clinical trials
  - Adaptive Clinical Trial Designs

- Visit symposium webpage at
  http://statistics.msi.meduniwien.ac.at/hp/small2014/
Symposium on small populations

Objectives of the joint symposia:

• To inform about the research plans of the three FP7 projects
• To facilitate the collaboration between FP7-projects and interaction with external stakeholders including EU FP7 representative, patient organizations, regulatory agencies, industry, ethics committee, …)
• To discuss status-quo of methodological issues in small populations research
• To discuss proposals for new and improved statistical design methodologies for clinical trials
• To train young researchers in this topic

WE WOULD BE GLAD IF YOU COULD COME!
HOW TO STAY IN CONTACT WITH IDEAL

- VISIT THE IDEAL WEBPAGE
  - http://www.ideal.rwth-aachen.de

- Get LinkedIn IDEAL – FP7 Project
  - http://www.linkedin.com/groups/IDEAL-FP7-Project-6556030

- Twitter @ideal_fp7
  - https://twitter.com/ideal_fp7
Many thanks for your patience!

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