Innovative statistical design methodologies for clinical trials in small populations focussing on rare diseases

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IDeAI Background

There is a pressing need to integrate a broad range of innovative methodologies improving clinical trials in the setting of small sample population groups (SPG).
The objective of this research is to produce methods of general applicability irrespective of indication by Integrated DEsign and AnaLysis of clinical trials in SPG (IDeAI) through a multidisciplinary closely collaborating consortium of researchers from European universities, research institutes and industry.

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EU Funding Initiative

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.

Multidisciplinary Framework involve all relevant stakeholders (including industry and patient advocacy groups) as appropriate. Ideally, results would lead to improvement of clinical trial guidelines. Collaboration with relevant organisations outside Europe is welcomed.

Expected Impact Cost efficient clinical trials deriving reliable results from trials in small population groups.

IDeAl - as EU funded project

Integrated DEsign and AnaLysis
of small population group trials

aims to refine the statistical methodology for clinical trials in small population groups by strictly following the concept of an improved integration of design, conduct and analysis of clinical trials from various perspectives.

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Who am I?

Ralf-Dieter Hilgers
Head of the Department of Medical Statistics at RWTH Aachen University
Coordinator of the IDeAl Project

- studied mathematics at RWTH Aachen University
- got my PhD at the statistical faculty of the University of Dortmund
- since 2001 head of the Department of Medical Statistics (IMSA) at the Medical Faculty, RWTH Aachen University
- research interest is in optimal design of experiments, randomization procedure and clinical trials
- expertise in teaching, consultation etc.

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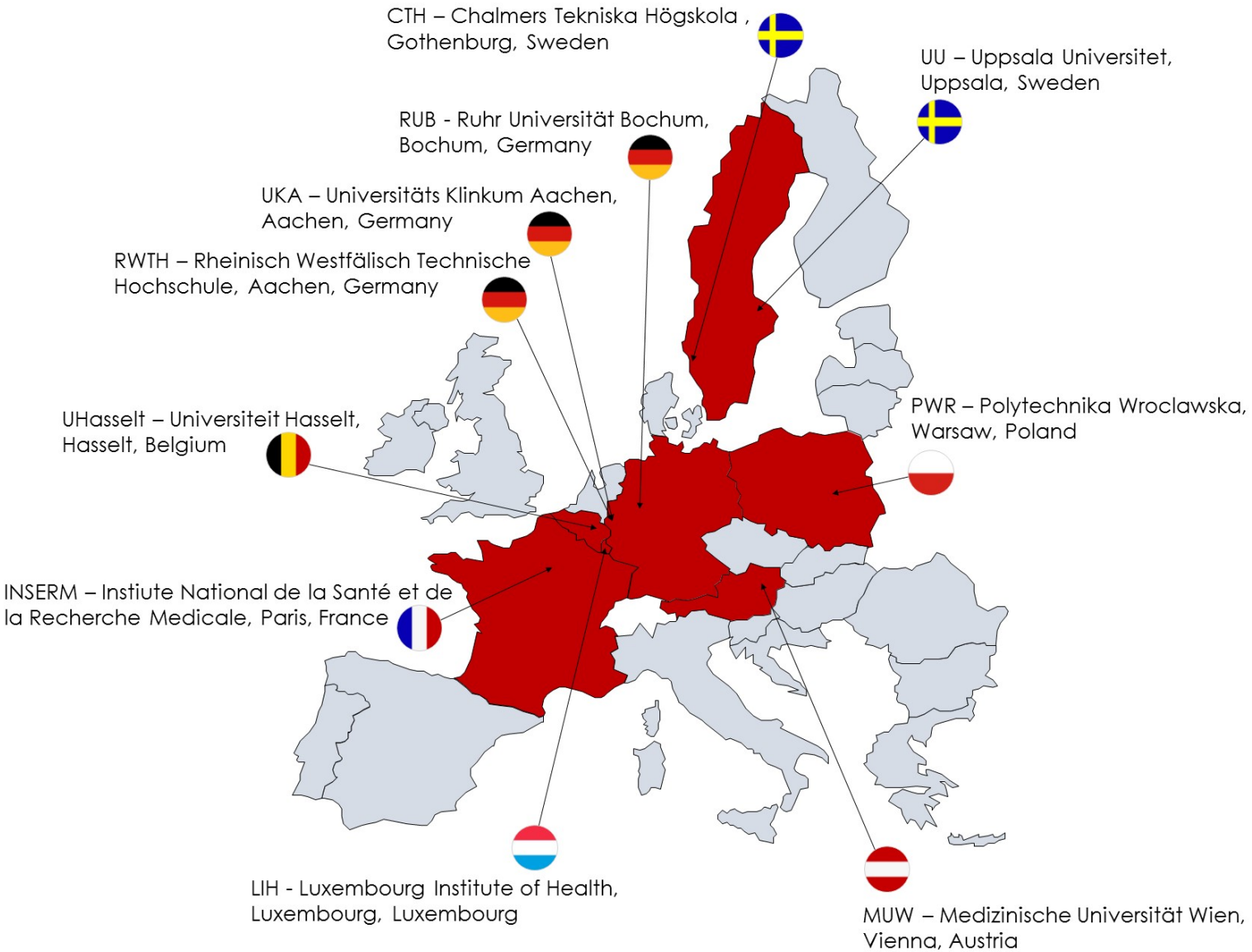
Partner of the IDeAI Project



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Who we are?

Carl-Frederik Burman

Holger Dette

Ralf-Dieter Hilgers

Malgorzata Bogdan

Mats O. Karlsson

Stephen Senn

Franz König

Geert Molenberghs

France Mentré

Christoph Male

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IDeAI - People

IDeAI Meeting in Paris, November 2014

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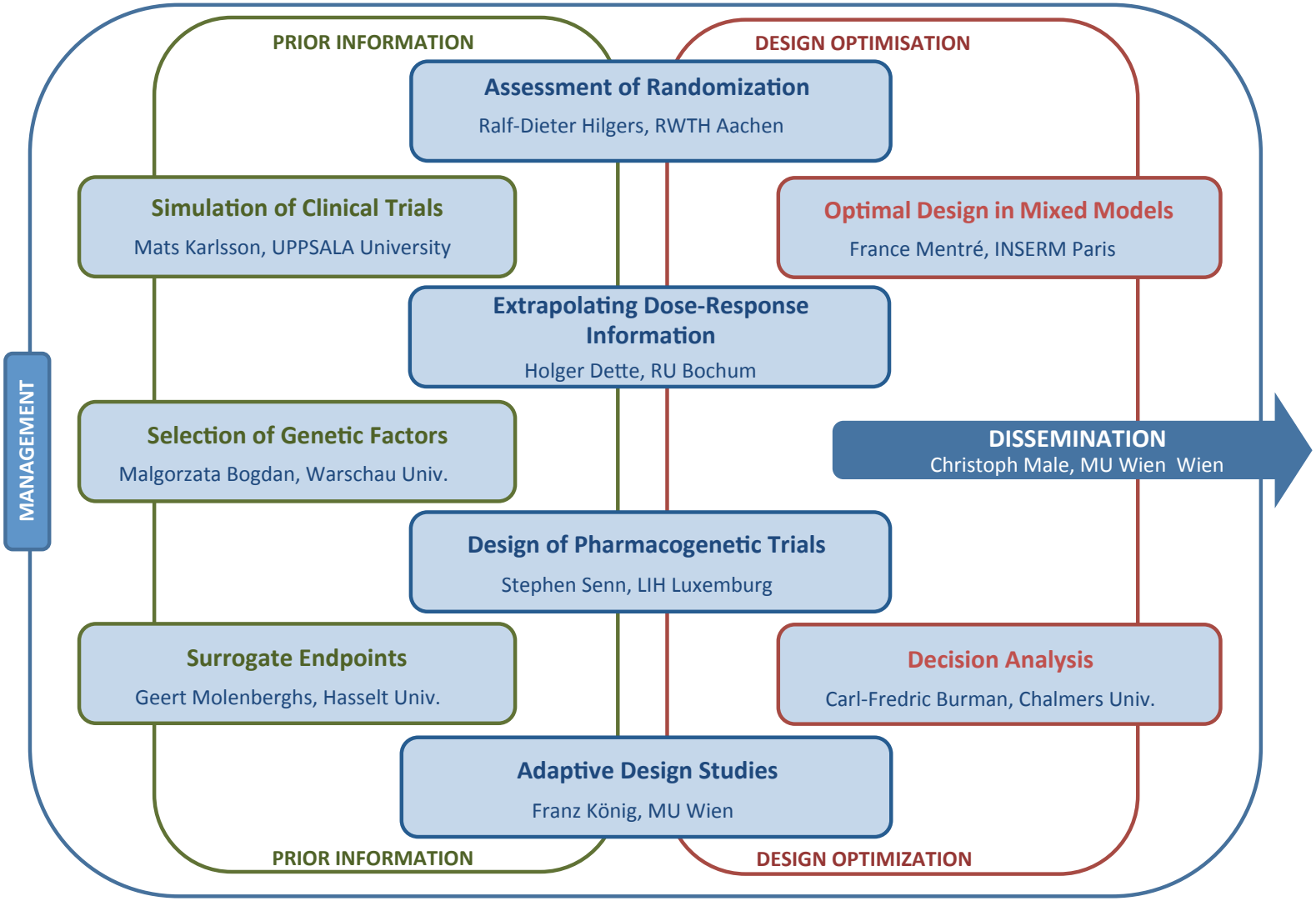
External Advisory Board

No	Name	Country
1	Segolene Aymé	(F)
2	Rosemary Bailey	(UK)
3	Paolo Baroldi	(USA)
4	Frank Bretz	(CH)
5	Tomasz Burzykowski	(USA)
6	Martin Forster	(UK)
7	Ralf Herold	(UK)
8	Chris Jennison	(UK)

No	Name	Country
9	Steven A. Julious	(GB)
10	Gerard Nguyen	(F)
11	Paolo Pertile	(I)
12	Gérard Pons	(F)
13	William F. Rosenberger	(USA)
14	Chiara Sabati	(USA)
14	Günther Schmalzing	(D)
14	Gernot Wassmer	(D)

Structure of the IDeAl Project



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IDeAI Work Program

1. **WP 2:** Assessment of randomisation procedures and randomisation based tests in SPG
2. **WP 3:** Extrapolating dose response information to SPG
3. **WP 4:** Adaptive design studies in SPG
4. **WP 5:** Optimal design in mixed models to analyse studies in SPG
5. **WP 6:** Design of pharmacogenetic SPG trials, incl. cross-over trials, n-of-1 trials and enrichment trials
6. **WP 7:** Simulation of clinical trials in SPG
7. **WP 8:** Genetic factors influencing the response to the therapy in SPG
8. **WP 9:** Decision analysis in SPG
9. **WP 10:** Biomarker surrogate endpoints in SPG
10. **WP 11:** Dissemination

EMA issues and interest - IDeAI project(s)

EMA interest	IDeAI - Workpackages
Extrapolation Standards of evidence	WP3: Extrapolating Dose-Response Information (*Holger Dette*) WP 4: Adaptive Design Studies (*Franz König*)
Data-driven decision-making	WP 9: Decision Analysis (*Carl Fredrik Burman*)
Understanding value of research	WP 6: Design of Pharmacogenetic Trials (*Stephen Senn*)
Multidisciplinary simulations	WP 7: Simulation of Clinical Trials (*Mats Karlsson*) WP 5: Optimal Design in Mixed Models (*France Mentré*)
Effects, bias randomisation	WP 10: Surrogate Endpoints (*Geert Molenberghs*) WP 2: Assessment of Randomization (*Ralf-Dieter Hilgers*)

IDeAl Output I

WP 2	We developed a new methodology for the selection of the best practice randomization procedure and subsequent analysis for a SPG CT taking possible bias into account.
WP 3	We developed a new optimized design and analysis strategy for comparing dose response profiles to extrapolate clinical trial results from a large to a small population.
WP 4	We developed statistical methods to adapt the significance level and allow confirmatory decision-making in clinical trials with vulnerable, small populations.
WP 5	We developed design evaluation methods enabling small clinical trials to be analysed through modelling of continuous or discrete longitudinal outcomes.
WP 6	We developed approaches to planning and analysing trials for identifying individual response and examining treatment effects in small populations.

IDeAl Output II

WP 7	We developed new methods for sample size calculation, type 1 error control, model averaging and parameter precision in SPG CT within non-linear mixed effects modelling.
WP 8	We developed new methods for identifying biomarkers and prognostic scores based on high dimensional genetic data in SPG CT.
WP 9	We evaluated how to optimise the overall value of drug development to patients, to regulators and to society under opacity in regulatory and payer rules as well as in very rare diseases.
WP 10	We developed methodology to evaluate potential surrogate markers and to analyse data from a small numbers of small trials, with emphasis on fast and easy computational strategies.

IDeAl Output

- 45 publications in peer reviewed journals (actual state)
- presentations at various conferences (among other at the FDA)
- workshops at different conferences
- organized conferences and sessions at conferences
- released various free available software programms
- input to regulatory guidelines
- study stays abroad program
- some input to design and analysis of rare disease clinical trials
- webinar series available via website
- regular newsletters

IDeAI - Network

- close contact to Kit Roes (asterix) and Nigel Stallard (InSPiRe)
- IRDiRC task force on small population clinical trials
- DIA small populations working group

asterix

IRDiRC
INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM

InSPiRe
Innovative methodology for small populations research

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What is going in the future?

- Prologantion accepted by the EC up the April 2017
- develop a synthesis statement of the three funded projects
- EMA (29.-30.03. 2017 London)

asterix

InSPiRe
Innovative methodology for small populations research

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Keep in touch with IDeAI

- VISIT THE IDeAI 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