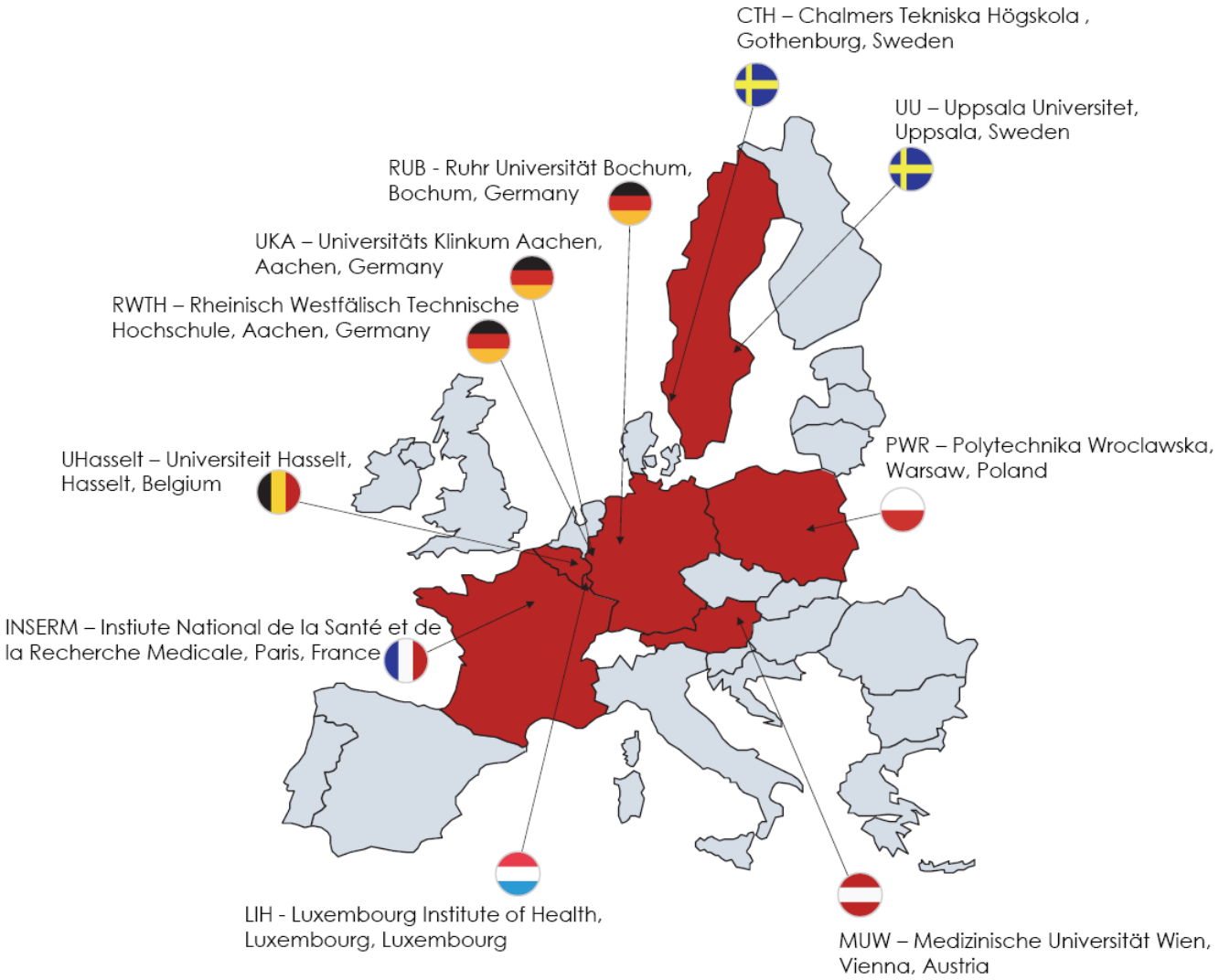
IDeAl NEWSLETTER ISSUE 3

AUGUST 2015



Impressum

Project duration:	1. November 2013 -31. October 2016
Project coordinator:	Ralf-Dieter Hilgers University Hospital Aachen - Department of Medical Statistics
Project webpage:	http://www.ideal.rwth-aachen.de/
Social networks:	Twitter @ https://twitter.com/ideal_fp7
	LinkedIn @ https://www.linkedin.com/groups/IDEAL-FP7-Project-6556030
Newsletter Editors:	Gerald Hlavin, Sergii Krasnozhon (Medical University of Vienna) David Schindler, Diane Uschner (University of Aachen)

INI Meeting

Several members of the IDeAl consortium got together at Isaac Newton Institute in Cambridge for one week (July 6th – 10th, 2015) to discuss mathematical implications for the design and analysis of experiments in healthcare. The meeting comprised two main parts: The first part was devoted to the fruitful exchange of the IDeAl consortium and EAB members, and the scientific community. F. Mentré, M.K. Riviere, S. Ueckert (INSERM), R.-D. Hilgers (UKA), and H. Dette (RUB) stimulated the discussions with talks from their cutting-edge research, and the EAB members C. Jennison, R. A. Bailey, S. Julious, and W. F. Rosenberger added presentations replete with experience form their areas of expertise. The second part was dedicated to the dialogue with stakeholders from industry and regulators from EMA. The second part of the meeting highlighted state-of-the-art design of experiments methodologies and how these can impact the wider societal health objectives. The broad audience was captivated by R.-D. Hilgers talk on the recent advances of the IDeAl project. F. König added an in-depth presentation about the newly developed approach for tests in dose-response studies. The meeting is expected to boost the advances in the field of Design and Analysis of Experiments in Healthcare, as well as the cooperation with regulatory sector.

In the following two tables the contributions of the IDeAl related presenters are listed:

Part I: Design and Analysis of Experiments in Healthcare		
F. Mentré (WP 5)	10 years of progress in population design methodology and applications	(Video)
M.K. Riviere (WP 5)	Evaluation of the Fisher information matrix in nonlinear mixed effects models using Monte Carlo Markov Chains	(Video)
S. Ueckert (WP 5)	Computation of the Fisher information matrix for discrete nonlinear mixed effects models	(Video)
R.-D. Hilgers (WP 2)	Assessment of randomization procedures based on single sequences under selection bias	(Video)
H. Dette (WP 3)	Optimal designs for correlated observations	(Video)
C. Jennison (EAB)	Designing an adaptive trial with treatment selection and a survival endpoint	(Video)
R. A. Bailey (EAB)	Designs for dose-escalation trials	(Video)
S. Julious (EAB)	Efficient study designs	
W. F. Rosenberger (EAB)	Randomization for small clinical trials	(Video)

Part II: Design of Experiments in Drug Development		
R.-D. Hilgers (WP 2)	IDeAL (Integrated DEsign and AnaLysis of small population group trials) - A Collaborative Approach between Industry and Academia	(Video)
F. König (WP 4)	Confirmatory Testing for a Beneficial Treatment Effect in Dose-Response Studies using MCP-Mod and an Adaptive Interim Analysis	(Video)

These and other talks can also be found on the websites of the Isaac Newton Institute (Part I) and the Turing Gateway to Mathematics (Part II).

IDeAl News posted on the webpage January 2015 until July 2015

January 2015

- 36 new orphan drugs approved by FDA in 2014
  - indicating gaining recognition of rare diseases in drug development
- EMA approved a record number of medicines for rare diseases in 2014
  - the highest number of marketing authorizations of orphan drugs in a year
- IBS joint Seminar with IDeAl mentioned in Biometric Bulletin
  - The seminar was organized jointly by the IDeAl project and the WBS.
  - The IBS Bulletin can be found here.

February 2015

- Rare Disease Day
  - took place in February to raise awareness about rare diseases and their impact on patients' lives
- Workshop on Design and Analysis of Experiments in Healthcare
  - This workshop is a follow-up to the 2011 six-month research programme on Design and Analysis of Experiments at INI, and is partly funded by IDEAL.

April 2015

- Ralf-Dieter Hilgers was nominated as IRDiRC Task Force Member
  - The IDeAl project has been identified as a key-player in the field of small population clinical trials, and will take part in the task force as a key-member.

May 2015

- IDeAl mentioned in April newsletter of Japanese agency PMDA
  - The Newsletter can be found here.

June 2015

- Austrian magazine “Profil” issues extensive article on Pediatrics
  - the article calls attention to the lack of drugs licensed for the tharapy of diseases in children

July 2015

- INI meeting in Cambridge was a big success
  - Several members of the IDeAl consortium got together at Isaac Newton Institute in Cambridge for one week (July 6th – 10th, 2015) to discuss mathematical implications for the design and analysis of experiments in healthcare.

July 2015: **INI Meeting on "Design and Analysis of Experiments in Healthcare"**

New Results

Articles in peer-reviewed journals

- Bauer, Peter, Frank Bretz, Vladimir Dragalin, Franz König, and Gernot Wassmer. "Twenty-five years of confirmatory adaptive designs: opportunities and pitfalls." *Statistics in medicine* (2015).
- Kennes, Lieven N., William F. Rosenberger, and Ralf-Dieter Hilgers. "Inference for blocked randomization under a selection bias model." *Biometrics* (2015).
- Abad, Ariel Alonso, Wim Van der Elst, and Geert Molenberghs. "Validating predictors of therapeutic success: A causal inference approach." *Statistical Modelling* (2015): 1471082X15586286.
- Lendrem, Dennis, Stephen J. Senn, B. Clare Lendrem, and John D. Isaacs. "R&D productivity rides again?."*Pharmaceutical statistics* 14, no. 1 (2015): 1-3.

Presentations

- Model selection approach for genome wide association studies. M. Bogdan, F. Frommlet, P. Szulc, H. Tuang. 2014 Dec 6-8. 7th International Conference of the ERCIM WG on Computational and Methodological Statistics. Pisa, Italy.
- "Innovative designs for confirmatory clinical trials - with emphasis on small population groups". C-F Burman, Swedish Society for Medical Statistics, 17 March 2015. Sweden
- A Linked Optimization Criterion for the Assessment of Selection and Chronological Bias in Randomized Clinical Trials. D. Schindler, R.-D. Hilgers. 2015 Mar 18. 61. Biometrisches Kolloquium. Dortmund, Germany.
- "An overview of new methods and tools for model building, evaluation and utilization" (invited). Mats O. Karlsson. 2015 Mar 18. International Society of Pharmacometrics, Lambertville, NJ, USA.
- Efficient tests for the similarity of dose response curves. K. Möllenhoff, H. Dette. 2015 Mar 18. 61. Biometrisches Kolloquium. Dortmund, Germany.
- 'Repligate': reproducibility in statistical studies. What does it mean and in what sense does it matter? (invited), S. Senn. 2015 Mar 27. John Nelder Workshop in Methdological Statistics. London, UK.
- Adaptive designs for confirmatory model based decisions using MCP-Mod. S. Krasnozhon. Symposium on Early Phase Clinical Trial Methodology. 2015 Apr 15-17.Paris, France
- Meta-analysis of rare (binary) events S.Senn. 2015 May 11. PSI Annual Conference. London, UK.
- "Pharmaceutical Phase III investments with uncertain reimbursement". S. Jobjörnsson, Kiel University. 28 May 2015. Kiel, Germany.
- 'Repligate.' Why and How Should We Care About Reproducing Study Results? (invided), S. Senn. 2015 May 23. 27th Convention of the Association for Psychological Science. New York, USA. (link to audio recording)
- "Late-Stage Pharmaceutical R&D for Rare Diseases under Two-Stage Regulation". S. Jobjörnsson, M. Forster, P. Pertile , C-F Burman, presented by P. Pertile. 16th European Health Economics Workshop. 2015 May 28-29. Toulouse, France.
- "Adaptive designs to select population, sample size and dose". C-F Burman. TFS Symposium. 2015 June 2. Copenhagen, Denmark.
- "Optimal and adaptive designs, when patients are scarce". C-F Burman. TFS Symposium. 2015 June 3. Stockholm, Sweden.

- Does size really not matter? Evaluation of treatment effects in subgroups and other small populations. (contribution to invited session), S. Senn. 2015 Jun 16. IBS-ROeS 2015. Milano, Italy.
- Evidence, Eminence and Extrapolation - Adjusted Levels of Evidence in Small Populations. G. Hlavin, F. König, C. Male, M. Posch, P. Bauer. IBS-ROeS 2015, Milano, Italy.
- "Optimizing the biomarker subpopulation strategy in late stage clinical development" (invited). T. Ondra, S. Jobjörnsson, B. Beckman, C-F Burman, F. König, N. Stallard & M. Posch, presented by C-F Burman. DIA 51st Annual Meeting. 2015 June 14-18. Washington DC, USA
- Response-Adaptive Randomization and Adaptive Combination Test for ClinicalTrials with Limited Number of Patients: Practical Guide. S. Krasnozhon. Workshop on Adaptive Designs and Multiple Comparison Procedures. 2015 Jun 24-26. Cologne, Germany.
- Adjusting multiplicity using safety data in many-one comparisons. G. Hlavin, F. König, P. Bauer. Workshop on Adaptive Designs and Multiple Comparison Procedures. 2015 Jun 24-26. Cologne, Germany.
- Exploring subgroups: when is enough, enough? S. Senn. 2015 Jun 29 - Jul 1. ISBS/DIA Symposium on Biopharmaceutical Statistics – “Big and Small Data: The Role of Statistics in Drug Development”. Beijing, China.
- Repeat after me! Bayes will not cure "the crisis of reproducibility". S. Senn. 2015 Jun 29 - Jul 1. ISBS/DIA Symposium on Biopharmaceutical Statistics – “Big and Small Data: The Role of Statistics in Drug Development”. Beijing, China.

- "Optimizing trial designs for targeted therapies" (invited). S. Jobjörnsson and T. Ondra. DIA Working Group on Small Populations. 2015 July 10.
- Randomisation: Misunderstanding, myths, and truth. S. Senn. 2015 August 5. Brussel Summer School of Mathematics, Université Libre de Bruxelles, Brussels, Belgium.

Conference Posters

- "Determination of Appropriate Settings in the Assessment of Parameter Uncertainty Distributions using Sampling Importance Resampling (SIR)". Anne-Gaëlle Dosne, Martin Bergstrand and Mats O. Karlsson. PAGE Meeting. 2015 Jun 2 – 5. Crete, Greece.
- "Quantifying drug effects in phase 2a anti-diabetic studies: Power and accuracy of four HbA1c models". Gustaf J. Wellhagen, Mats O. Karlsson and Maria C. Kjellsson. PAGE Meeting. 2015 Jun 2 – 5. Crete, Greece.
- "Influence of clinical trial design to detect drug effect in systems with within subject variability". Chenhui Deng, Elodie L. Plan and Mats O. Karlsso. PAGE Meeting. 2015 Jun 2 – 5. Crete, Greece.

Comments

- Comment on errorstatistics.com: Double Jeopardy?: Judge Jeffreys Upholds the Law (sequel to the pathetic P-value) by S. Senn. [posted on 2015-05-09]
- Comment on errorstatistics.com: The pathetic p-value by S. Senn. [posted on 2015-03-16]

Statistical Software Programs

- R package on the Prediction of Therapeutic Success. Wim Van der Elst, Ariel Alonso & Geert Molenberghs. [published 2015-04-27]
- R package for the estimation of within subject correlations based on linear mixed effects models. Wim Van der Elst, Geert Molenberghs, Dieter Hilgers, & Nicole Heussen. [published 2015-04-29]
- Perl-speaks-NONMEM Version 4.4.0. Kajsa Harling, Rikard Nordgren, Mats O. Karlsson and Andrew C. Hooker. [released 2015-04-20]
    - *A new version of the randtest tool and improved methodology for sampling-importance-resampling (SIR) were included.*

Upcoming IDeAl Events

- September 21 – 25, 2015; Eighth International Workshop on Simulation; Vienna, Austria
    - Invited session "Statistical Aspects in Small Population Group Trials" organized by RD Hilgers
- November 5 – 6, 2015; **IDEAL ANNUAL MEETING 2015**; Leuven, Belgium

Abstracts of Articles in Peer-Reviewed Journals

Bauer, Peter, Frank Bretz, Vladimir Dragalin, Franz König, and Gernot Wassmer. "Twenty-five years of confirmatory adaptive designs: opportunities and pitfalls." Statistics in medicine (2015).

‘Multistage testing with adaptive designs’ was the title of an article by Peter Bauer that appeared 1989 in the German journal *Biometrie und Informatik in Medizin und Biologie*. The journal does not exist anymore but the methodology found widespread interest in the scientific community over the past 25 years. The use of such multistage adaptive designs raised many controversial discussions from the beginning on, especially after the publication by Bauer and Köhne 1994 in *Biometrics*: Broad enthusiasm about potential applications of such designs faced critical positions regarding their statistical efficiency. Despite, or possibly because of, this controversy, the methodology and its areas of applications grew steadily over the years, with significant contributions from statisticians working in academia, industry and agencies around the world. In the meantime, such type of adaptive designs have become the subject of two major regulatory guidance documents in the US and Europe and the field is still evolving. Developments are particularly noteworthy in the most important applications of adaptive designs, including sample size reassessment, treatment selection procedures, and population enrichment designs. In this article, we summarize the developments over the past 25 years from different perspectives. We provide a historical overview of the early days, review the key methodological concepts and summarize regulatory and industry perspectives on such designs. Then, we illustrate the application of adaptive designs with three case studies, including unblinded sample size reassessment, adaptive treatment selection, and adaptive endpoint selection. We also discuss the availability of software for evaluating and performing such designs. We conclude with a critical review of how expectations from the beginning were fulfilled, and – if not – discuss potential reasons why this did not happen.

Kennes, Lieven N., William F. Rosenberger, and Ralf-Dieter Hilgers. "Inference for blocked randomization under a selection bias model." Biometrics (2015).

We provide an asymptotic test to analyze randomized clinical trials that may be subject to selection bias. For normally distributed responses, and under permuted block randomization, we derive a likelihood ratio test of the treatment effect under a selection bias model. A likelihood ratio test of the presence of selection bias arises from the same formulation. We prove that the test is asymptotically chi-square on one degree of freedom. These results correlate well with the likelihood ratio test of Ivanova et al. (2005, *Statistics in Medicine* **24**, 1537–1546) for binary responses, for which they established by simulation that the asymptotic distribution is chi-square. Simulations also show that the test is robust to departures from normality and under another randomization procedure. We illustrate the test by reanalyzing a clinical trial on retinal detachment.

Abad, Ariel Alonso, Wim Van der Elst, and Geert Molenberghs. "Validating predictors of therapeutic success: A causal inference approach." Statistical Modelling (2015): 1471082X15586286.

In personalized medicine medical decisions, practices and/or products are tailored to the individual patient. The idea is to provide the right patient with the right drug at the right dose at the right time. However, our current lack of ability to predict an individual patient's treatment success for most diseases and conditions is a major challenge to achieve the goal of personalized medicine. In the present work, we argue that many of the techniques often used to evaluate predictors of therapeutic success may not be able to answer the relevant scientific questions and we propose a new validation strategy based on causal inference. The methodology is illustrated using data from

a clinical trial in opiate/heroin addiction. The user-friendly R library *EffectTreat* is provided to carry out the necessary calculations.

Lendrem, Dennis, Stephen J. Senn, B. Clare Lendrem, and John D. Isaacs. "R&D productivity rides again?."Pharmaceutical statistics 14, no. 1 (2015): 1-3.

A recent analysis of R&D productivity suggests that there are grounds for 'cautious optimism' that the industry 'turned the corner' in 2008 and is 'on the comeback trail'. We believe that this analysis is flawed and most probably wrong. We present an alternative analysis of these same data to suggest that the industry is not yet 'out of the woods' and suggest that many of the systemic issues affecting pharmaceutical R&D productivity are still being resolved.

The research leading to these results has received funding from the European Union Seventh Framework Programme under grant agreement n° 602552.