IDeAl NEWSLETTER ISSUE 1
SEPTEMBER 2014

Overview

Project Start:	1. November 2013 (duration 3 years)
Projected end:	31. October 2016
Project coordinator:	Ralf-Dieter Hilgers University Hospital Aachen - Department of Medical Statistics
Project partners:	10 European universities / 8 EU countries
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 (Medical University of Vienna) Sergii Krasnozhon (Medical University of Vienna) David Schindler (University of Aachen) Diane Uschner (University of Aachen)

Introduction

There exist more than 7000 rare diseases worldwide and the European Society of Paediatric Oncology stated that 75% of rare diseases affect children and 30% of rare disease patients die before the age of five.

Standard statistical methods for proving efficacy and safety of therapies fail to provide cost-efficient and reliable results in small populations. Thus 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 (IDeAl) through a multidisciplinary closely collaborating consortium of researchers from European universities, research institutes and industry.

The consortium works in 11 WPs, focusing on assessment of randomization procedures, extrapolating dose-response information, investigation of adaptive designs, optimal designs in mixed models, pharmacogenetic designs, simulation of clinical trials, genetic factors influencing the response, decision analysis and biomarker surrogate endpoints as well as WPs on project management and dissemination of results. Relevant stakeholder concerns (patient needs, regulatory issues, reimbursement, clinical feasibility) are continuously monitored by an external Scientific Advisory Board. Because of its integrative structure, this research program extends previous approaches, which focus on a certain methodology only. In its totality, the WPs constitute a logically coherent set of methodologies that is of sufficient breadth to tackle these important, multidisciplinary challenges. By combining, enhancing and developing different statistical methodologies and assessment methods, this research program will impact the scientific discussion in promoting efficient statistical methodology for clinical trials in SPG, also in view of existing regulatory guidance in the EU.

Dissemination of the Results

A public website (http://www.ideal.rwth-aachen.de/) shall ensure a central and freely accessible repository, informing about the project, its content, and its progress. It is used for regular updates on the Consortium´s activities and highlight major achievements. The public webpage lists all published and working papers of the Consortium and all open-source software on IDeAl clinical trial designs (e.g., R-packages or SAS-code).

Furthermore a bi-annual electronic newsletter is accessible at network website to inform all interested parties on the progress of the project and on all up-coming events, conferences publications and journals. Anyone can freely subscribe on the IDeAl webpage to receive the newsletter by email. It is also possible to follow IDeAl on twitter and LinkedIn.

Overview Scientific Work Packages

Work package title	Lead Participant	Leader
Assessment of randomisation procedures and randomisation based tests in small population groups	University Hospital Aachen - Department of Medical Statistics (IMSA)	Ralf-Dieter Hilgers
Extrapolating dose-response information to small population groups	Ruhr-University Bochum - Faculty of Mathematics	Holger Dette
Adaptive design studies in small population groups	Medical University of Vienna - CEMSIIS - Section of Medical Statistics	Franz König
Optimal design in mixed models to analyse studies in small population groups	French National Institute of Health and Medical Research	France Mentré
Design of pharmacogenetic small population group trials including cross-over trials, n-of-1 trials and enrichment trials	CENTRE DE RECHERCHE PUBLIC DE LA SANTÉ - Competence Center for Methodology and Statistics	Stephen Senn
Simulation of clinical trials in small population groups	UPPSALA UNIVERSITET Department of Pharmaceutical Biosciences	Mats O. Karlsson
Genetic factors influencing the response to the therapy in small population group trials	Wroclaw University of Technology - Institute of Mathematics and Computer Science	Malgorzata Bogdan
Decision analysis in small population groups	Chalmers University of Technology - Mathematical Sciences	Carl-Frederik Burman
Biomarker surrogate endpoints in small population groups	UNIVERSITEIT HASSELT & KU LEUVEN - Leuven Centre for Biostatistics and statistical Bioinformatics	Geert Molenberghs

Supportive Work Packages

Work package title	Lead Participant	Leader
Project Management and Coordination	RWTH Aachen University	Eva Haas
Dissemination	Medical University of Vienna - Department of Paediatrics and Adolescents	Christoph Male

For further information on

- work packages visit http://www.ideal.rwth-aachen.de/?page_id=58
- project partners visit http://www.ideal.rwth-aachen.de/?page_id=60

External Advisory Board

The scientific work is accompanied and supervised by an international external advisory board, which includes representatives from academia, industry, regulatory agencies (European Medicines Agency) and patient representatives. The advisory board has regular F2F meetings supported by teleconferences. For any further questions concerning the advisory board, please contact the project leader RD Hilgers.

Bailey, Rosemary, UK

Baroldi, Paolo, I

Bretz, Frank, CH

Burzykowski, Tomasz, BE

Forster, Martin, UK

Herold, Ralf, UK

Jennison, Christopher, UK

Julious, Steven, UK

Llinares, Jordi, UK

Nguyen, Gerard, FR

Pertile, Paolo, IT

Pons, Gerard, FR

Rosenberger, William, USA

Sabatti, Chiara, USA

Schmalzing, Günther, DE

Wassmer, Gernot, DE

IDeAl News till August 2014

September 2013

[International research team develops new methods for therapy evaluation in rare diseases.](#)

November 2013

[Social Networks](#)

December 2013

[Input to EMA guideline](#)

January 2014

[Input to EMA guideline on covariates](#)

[Registration opens for joint EMA/FDA/MHLW-PMDA orphan medicinal product workshop](#)

February 2014

[Talk on Model Selection approaches](#)

[Symposium on rare diseases](#)

[DIA ADSWG meeting](#)

March 2014

[European Conference of Rare Diseases & Orphan Products](#)

July 2014

[First External Advisory Board Meeting was a Success](#)

[Young Scientist Meeting was a great Success](#)

[Symposium on Small Population Groups successful](#)

[Press Reviews of the Symposium on Small Populations](#)

August 2014

[Workshop on Design and Analysis of Experiments in Healthcare](#)

Results achieved until October 2014

Articles in peer-reviewed journals

- Tamm, M.; Hilgers, R.-D.: Chronological bias in randomized clinical trials arising from different types of unobserved time trends. 2014. Methods Inf Med. (to appear)
- Senn, S..: [A note regarding meta-analysis of sequential trials with stopping for efficacy.](#) Pharm Stats 14 July 2014 [published on IDeAl webpage on 2014-08-13].
- Koenig F, Slattery J, Groves T, Lang T, Benjamini Y, Day S, Bauer P, Posch M.: [Sharing clinical trial data on patient level: Opportunities and challenges.](#) Biom J. 2014 Jun 18. doi: 10.1002/bimj.201300283. [Epub ahead of print] [Abstract](#) [published on IDeAl webpage on 2014-06-25].
- Gewandter JS, Dworkin RH, Turk DC, McDermott MP, Baron R, Gastonguay MR, Gilron I, Katz NP, Mehta C, Raja SN, Senn S, Taylor C, Cowan P, Desjardins P, Dimitrova R, Dionne R, Farrar JT, Hewitt DJ, Iyengar S, Jay GW, Kalso E, Kerns RD, Leff R, Leong M, Petersen KL, Ravina BM, Rauschkolb C, Rice AS, Rowbotham MC, Sampaio C, Sindrup SH, Stauffer JW, Steigerwald I, Stewart J, Tobias J, Treede RD, Wallace M, White RE.: [Research designs for proof-of-concept chronic pain clinical trials: IMMPACT](#)

recommendations. Pain. 2014 May 24. pii: S0304-3959(14)00258-9. doi: 10.1016/j.pain.2014.05.025. [Epub ahead of print] Review. PMID: 24865794. http://www.sciencedirect.com [published on IDeAl webpage on 2014-06-25].

- Dworkin RH, McDermott MP, Farrar JT, O'Connor AB, Senn S.: Interpreting patient treatment response in analgesic clinical trials: implications for genotyping, phenotyping, and personalized pain treatment. Pain. 2014 Mar;155(3):457-60. doi: 10.1016/j.pain.2013.09.019. Epub 2013 Sep 23. No abstract available.http://www.sciencedirect.com [published on IDeAl webpage on 2014-06-25].
- Rose K, Senn S.: Drug development EU paediatric legislation, the European Medicines Agency and its Paediatric Committee-adolescents' melanoma as a paradigm. Pharm Stat. 2014 Jun 6. doi: 10.1002/pst.1623. [Epub ahead of print] PMID: 24903307 http://onlinelibrary.wiley.com [published on IDeAl webpage on 2014-06-25].
- Bauer P, König F.: The risks of methodology aversion in drug regulation. Nat Rev Drug Discov. 2014 May;13(5):317-8. doi: 10.1038/nrd4319. Review. http://www.nature.com/nrd/journal/v13/n5/full/nrd4319.html [published on IDeAl webpage on 2014-04-23].
- Graf A, Bauer P, Glimm E, Koenig F.:Maximum type 1 error rate inflation in multiarmed clinical trials with adaptive interim sample size modifications. Biometrical Journal 2014. Early View. DOI: 10.1002/bimj.201300153. http://onlinelibrary.wiley.com/doi/10.1002/bimj.201300153/full [published on IDeAl webpage on 2014-04-23].

Presentations

- Confirmatory testing for a beneficial treatment effect in dose-response studies using MCP-Mod and an adaptive interim analysis. Frank Bretz and Franz König. KOL Lecture Series on Adaptive Designs: Friday Sept. 12, 2014.
- Confirmatory testing for a beneficial treatment effect in dose-response studies using MCP-Mod. F König, B Bornkamp, F Bretz, E Glimm. Contributed Talk. ISCB 2014, 24-27 Aug, 2014. Vienna, Austria.
- Mastering variation: variance components and personalised medicine. S.Senn. Contributed Talk. [presented 2014-08-25 at ISCB Vienna]
- Assessment of chronological bias in randomized controlled clinical trials. M. Tamm. Contributed Talk. [presented 2014-08-25 at ISCB Vienna]
- "IDEAL – Integrated Design and Analysis of Small Population Group Trials". Ralf-Dieter Hilgers. Symposium on Small Populations. 1-2 July 2014. Vienna, Austria.
- Break out session on clinical and statistical issues in modeling and extrapolation. C Male. Symposium on Small Populations. 1-2 July 2014. Vienna, Austria.
- Break out session on the role of surrogate endpoints in small clinical trials. Wim Van der Elst. Symposium on Small Populations. 1-2 July 2014. Vienna, Austria.
- The role of extrapolation in regulatory decision making: experience from the EMA pediatric committee PDCO. Christoph Male. Symposium on Small Populations. 1-2 July 2014. Vienna, Austria.
- Pharmacometrics – a useful methodology in small clinical trials. Kristin Karlsson. Symposium on Small Populations. 1-2 July 2014. Vienna, Austria.
- Lightning Talks – various topics. G. Hlavin, S. Krasnozhon, K. Kerkmann, D. Uschner, D. Schindler, M. Tamm, A. Araujo, D. Brzyski, P. Sobczyk, M.-K. Riviere, C. Louenan, K. Karlsson, A.-G. Dosne, S. Jobjörnsson [presented 2014-06-30 at IDeAl YSM Vienna]
- Overcoming Resistance: Trials, Tribulations and Treatments. S. Senn. Invited Talk. [presented 2014-07-02 in Freiburg, Germany]
- A picture is worth a 1000 words – usually. Communicating Complex Statistical Concepts. S. Senn. Invited Talk.

- Flexibility in confirmatory clinical trials – what is for free? Workshop "Adaptive Designs and Multiple Testing Procedures" of the Joint Working Group (Section) of the ROeS and the German Region of the IBS. P. Bauer. Invited Keynote Talk. [presented 2014-06-05+06 in Basel, Switzerland]
- Adaptive designs for subgroup analysis optimizing utility functions. Workshop "Adaptive Designs and Multiple Testing Procedures" of the Joint Working Group (Section) of the ROeS and the German Region of the IBS. F. König. Invited Keynote Talk. [presented 2014-06-05+06 in Basel, Switzerland]
- Flexibility in confirmatory clinical trials – what is for free? International Clinical Trials' Day. P. Bauer. Invited Talk. [presented 2014-05-20 in Luxembourg]
- IDEAL Integrated Design and Analysis of small population group trials. RD Hilgers, CF Burman, F Koenig. DIA ADSWG Meeting. [presented 2014-02-28]

Short Courses

- ISCB Short Course in "Novel approaches to multiple test problems, with applications to adaptive designs and dose finding". Frank Bretz & Franz König. 27-28 November 2014. Budapest, Hungary.
- Summer school "Adaptive Designs and Multiple Testing in Clinical Trials". Franz König and Martin Posch. Universtat Politécnica de Catalunya. 8-10 July, 2014. Bareclona, Spain.
- Surrogate marker evaluation in clinical trials. Wim van der Elst. Symposium on Small Populations. July 2014. Vienna. Austria
- Randomisation and Stratification in clinical trials. Ralf-Dieter Hilgers, Armin Koch. Symposium on Small Populations. July 2014. Vienna. Austria
- Adaptive Clinical Trial Designs. Franz König, Martin Posch, Gernot Wassmer. Symposium on Small Populations. July 2014. Vienna. Austria
- Supporting the pathways to trials for rare diseases: Clinical trial design and other considerations. Part 1: Clinical trial designs for small population group trials. RD Hilgers. ECRD 2014. Invited Workshop. [presented 2014-05-09]

Comments

- Comment on IMI 2 Strategic Research Agenda: Aiming to Make a Real Impact on Everyday Healthcare and Patients by S. Senn. [submitted 2014-07-09]
- Comment on errorstatistics.com: Responder despondency: myths of personalized medicine by S. Senn. [submitted 2014-07-26]

Conference Posters

- Adaptive two-stage bioequivalence trials with early stopping and sample size re-estimation. F König, M Wolfsegger, T Jaki, H Schütz, G Wassmer. Conference Poster. ISCB 2014, 24-27 Aug, 2014. Vienna, Austria.
- Adaptive designs for confirmatory model based decisions using MCP-Mod. S Krasnozhon, A Graf, B Bornkamp, F Bretz, G Wassmer, F König. Conference Poster. ISCB 2014, 24-27 Aug, 2014. Vienna, Austria.
- Comparison of different allocation procedures in clinical trials in small population groups with respect to accidental and selection bias. D. Schindler, D.Uschner. Conference Poster. [presented 2014-08-25 at ISCB Vienna]
- Evidence, Eminence,and Extrapolation: Adapted Levels of Evidence for Small Populations. G. Hlavin. Conference Poster. [presented 2014-08-25 at ISCB Vienna]
- Integrated Design and Analysis of small population group trials. RD Hilgers. ECRD 2014.[presented 2014-05-09]

Input to Regulatory documents

- Comment on „Draft Guideline on the investigation of subgroups in confirmatory clinical trials (EMA/539146/2013)" by Stephen Senn, Franz König, Ralf-Dieter Hilgers and Geert Molenberghs.[submitted 2014-07-25]
- Comment on 'Draft guideline on adjustment for baseline covariates' (EMA/295050/2013) issued by Ralf-Dieter Hilgers. [submitted 2013-12-31]
- Comment on 'Draft qualification opinion of MCP-Mod as an efficient statistical methodology for model-based design and analysis of phase-II dose-finding studies under model uncertainty' (EMA/CHMP/SAWP/592378/2013) issued by Stephen Senn. [submitted 2013-11-21]

Press Releases

- Project Start [released 2013-09-06]
- FP7 Symposium on Small Populations [released 2014-02-28]

Conferences

- Symposium Vienna. [Date: 2014-07-01 to 2014-07-02]
- Kick-Off Meeting [Date: 2013-11-06 to 2013-11]

Statistical Software Programs

- R-Code to calculate worst case type I error inflation in multiarmed clinical trials [published 2014-04-23]
- R package on Surrogate Markers [published 2014-03-18]

Upcoming IDeAl Events

- **Next Annual IDeAl meeting in Paris:** November 3-4, 2014.
- ISCB Short Course in "Novel approaches to multiple test problems, with applications to adaptive designs and dose finding". Frank Bretz & Franz König. 27-28 November 2014. Budapest, Hungary.
- 2 October Copenhagen, DSBS & FMS 'Open data and closed minds'
- CRP-Santé, Luxembourg: Intermediate statistics for life scientists. Stephen Senn, 7& 8 October 2014. http://www.crp-sante.lu/en/Training-Workshops/Content/Technical-workshops
- Stratified Medicine Meeting, London: Variability in drug response. Stephen Senn, 23 October 2014 http://www.uk-pgx-stratmed.co.uk/index.php/latest-events/icalrepeat.detail/2014/10/23/8/-/defining-drug-response-for-stratified-medicine?filter_reset=1
- ExIStA and RSS meeting, Exeter: **Mastering variation: Variance components and personalised medicine. Stephen Senn.** 24 October 2014 http://emps.exeter.ac.uk/research/mathematics/eisa/events/seminaroct14-event/
- MediasRes meeting Bern, Course on Statistical Issues in Drug Development. Stephen Senn. 7 November 2014

- Wellcome Clinical Research Trust. Edinburgh: Course on Cross-over Trials in Clinical Research. Stephen Senn. 17-18 November 2014. http://www.eventbrite.co.uk/e/wtcrf-cross-over-trials-in-clinical-research-2-day-course-tickets-11958230389