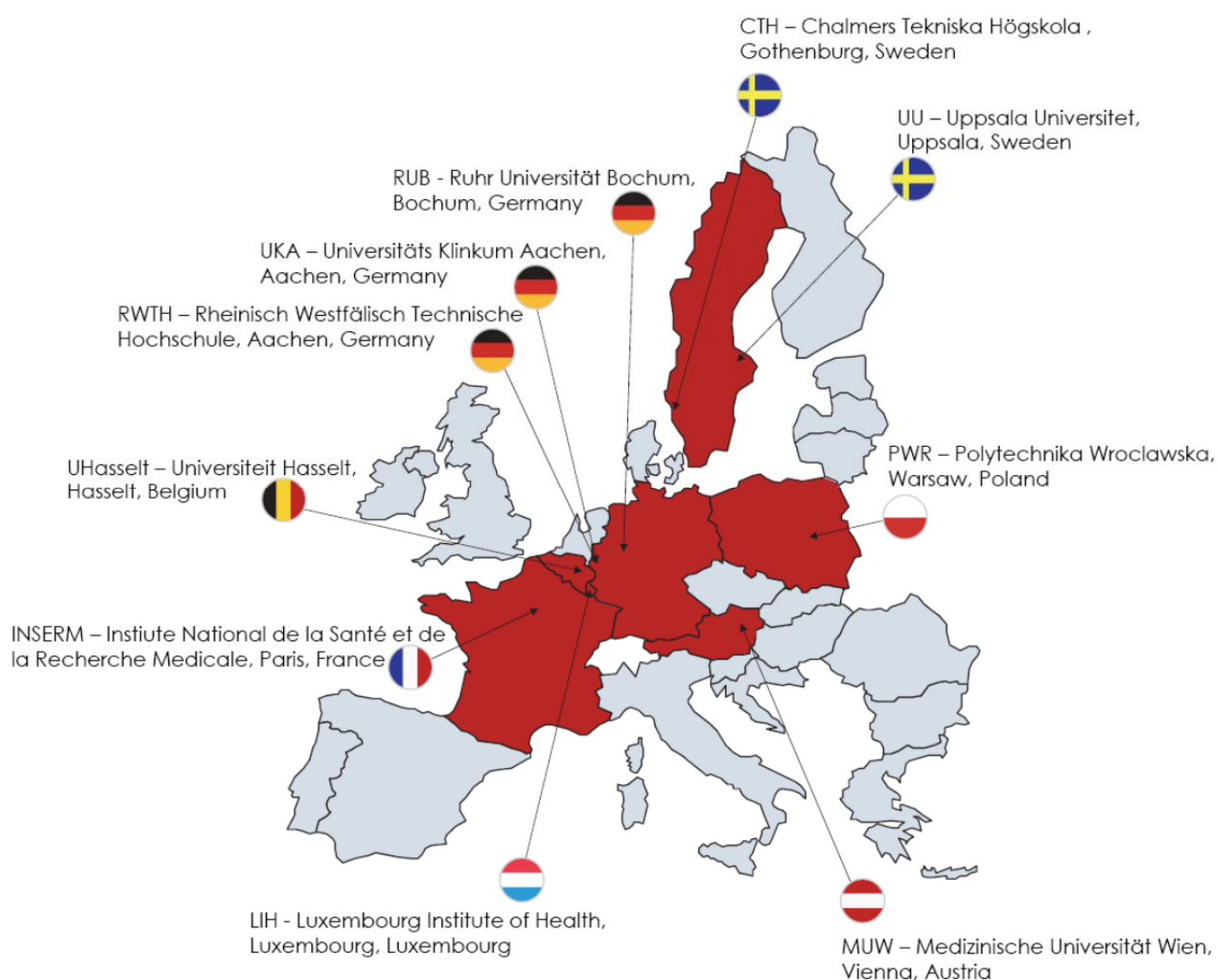




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Impressum

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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
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Selected Highlights

IDeAI invited to EU meetings in Malta

From 19th to 20th of March Ralf-Dieter Hilgers, Coordinator of the IDEAL Project, was invited to represent the EU FP7 funded IDeAI project at the Strategic Review and Learning meeting of the Committee of Orphan Medicinal Products (COMP) of the European Medicines Agency (EMA) and the Conference on the Development and Access of Medicines for Rare Diseases conducted by the Malta Medicines Authority (MMA), COMP of EMA, EURORDIS and IMI under the auspices of Maltese EU 2017 Presidency.

The workshop was part of a series of meetings of the Medicines Authority during the Maltese Presidency and was held in parallel with the Informal Health Minister's meeting and the meeting of the Committee for Orphan Medicinal Products at the Grand Master's Palace.

Prof. Hilgers gave an overview on the IDeAI project highlighting the newest results coming out of the IDeAI project titled

“Innovative statistical design methodologies for clinical trials in small populations
focusing on rare diseases I & II”

at the Strategic Review and Learning meeting of the COMP.

The meeting served as an excellent opportunity to discuss innovative statistical design and analysis methods with EU stakeholders. At the Conference on the Development and Access of Medicines for Rare Diseases , March 21th, Dr. Irene Norstedt (Head of Innovative and Personalised Medicine Unit, European Commission) mentioned the IDeAI project as an successful and unique examples of FP7 collaborative projects.





FP7 Small-population research methods projects and regulatory application workshop at the European Medicines Agency

The three EU FP7 projects Asterix, IDeAl and InSPiRe held a joint dissemination workshop at the European Medicines Agency (EMA) on 29 & 30 March 2017 as all three projects will end later this year.

The main goal of the workshop was to translate and promote novel methodologies of all three EU FP7 funded projects into tangible recommendations. The research should advance clinical research and the development of new treatments in small populations, such as in rare diseases, children or targeted therapies for personalized medicine.

Results from five main areas were presented and discussed at the workshop:

- Evidence synthesis
- Extrapolation
- Level of evidence and decision theoretic aspects
- Study Endpoints and statistical analysis
- Innovative designs, Pharmacometrics, modelling and optimal designs

The IDeAl consortium contributed presentations by Ralf-Dieter Hilgers, Stephen Senn, Ségolène Aymé, Franz König, Holger Dette, Carl-Fredrik Burman, Geert Molenberghs, France Mentré and Mats Karlsson. In addition to presentations all sessions included discussants from patient organisations, academic statisticians, clinical trial methodologists, clinical researchers, pharmaceutical industry, HTAs and regulators.

As a special highlight, the meeting was broadcasted on the EMA website and, thus, interested parties from all over the world could follow the intensive discussions. The EMA kindly offered to publish all slides and videos of the workshop on its webpage.

Many thanks to the EMA (particularly to Ralf-Herold, Cecile Ollivier, Frank Petavy and Isabel Perez) for the great support and hosting the workshop! Dieter Hilgers and Franz König helped as members of the Scientific Coordinating committee to shape the structure and content of the meeting.

For the agenda, slides and links to the videos visit the EMA webpage at http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2017/02/event_detail_001393.jsp&mid=WC0b01ac058004d5c3



**Many thanks to Asterix, Inspire and EMA
for the excellent collaborations in the last three years!**





IDeAI Webinar Series

In 2016 we launched the IDeAI webinar series to present the main outputs and deliverables of each scientific work package. In this online series the IDeAI researchers presented their main results in an easily accessible fashion over the web using Adobe Connect. The series started with a general introduction by coordinator Prof. Ralf-Dieter Hilgers. Then each work-package leader of IDeAI presented the main achievements and findings in a non-technical way linking them to an example in small populations (e.g., in clinical studies for drug development of rare diseases, pediatrics, etc). The series was concluded by a webinar of the work package dissemination summarizing the highlights of the whole project. All presentations can be accessed via the IDeAI webpage at http://www.ideal.rwth-aachen.de/?page_id=1732 . At the [IDeAI YouTube channel](#) you can watch the recordings of the webinar series.

WP-Leader	Work Package	Working Title for the presentation
Dieter Hilgers	Overview on IDEAL and Introduction to Webinar Series	The IDeAI Webinar Series (I) - Introduction
Dieter Hilgers	WP2: Assessment of randomisation procedures and randomisation based tests in small population groups	Selection of a Randomization Procedure Does it matter? How it works!
Mats Karlsson	WP7: Simulation of clinical trials in small population groups	A sampling importance resampling procedure for estimating parameter uncertainty
Holger Dette	WP3: Extrapolating dose-response information to small population groups	Statistical inference for comparing small population groups
Geert Molenberghs	WP10: Biomarker surrogate endpoints in small population groups	Pseudo-likelihood and Split-sample Methods in Small and Very Large Studies: (FP7-IDEAL & ExaScience)
Franz König	WP4: Adaptive design studies in small population groups	Adaptive level of evidence
Stephen Senn	WP6: Design of pharmacogenetic small population group trials including cross-over trials, n-of-1 trials and enrichment trials	A little bit me, a little bit you: N of 1 trials, random effects and shrinkage estimators
France Mentré	WP5: Optimal design in mixed models to analyse studies in small population groups	Using Hamiltonian Monte Carlo to design clinical trials with longitudinal data
Malgorzata Bogdan	WP8: Genetic factors influencing the response to the therapy in small population group trials	Identifying genetic factors influencing important patient's characteristics
Carl-Frederik Burman	WP9: Decision analysis in small population groups	Optimal decisions and stakeholder interactions
RD Hilgers & F König	Dissemination	Dissemination



Selected IDeAI News posted on the IDeAI website from July 2016 to March 2017

2016

July

- [Ralf-Dieter Hilgers publishes a joint paper on new developments for small population group trials](#) together with the coordinators of the two other FP7 projects Asterix (Kit Roes) and Inspire (Nigel Stallard). Hilgers, R. D., Roes, K., and Stallard, N. '[Directions for new developments on statistical design and analysis of small population group trials.](#)' Orphanet Journal of Rare Diseases. 2016.

August

- [IDeAI at ISCB 2016 in Birmingham](#)
IDeAI researchers present their latest results at the conference of the International Society of Clinical Biostatistics in Birmingham 2016. Topics range from Extrapolation (Kathrin Möllenhoff, Gerald Hlavin), to Adaptive Designs (Franz König), N-of-One-Designs (Stephen Senn), Quantification (Tanja Berger), Randomization (Ralf-Dieter Hilgers, David Schindler, Marcia Rückbeil), Randomization Based Inference in the presence of missing values (Nicole Heussen) and Selection Bias (Diane Uschner).

September

- [First IDeAI Video Tutorial is now Online!](#)
An online tutorial on how to Generate Randomization Sequences for a Clinical Trial with randomizeR has been published on the IDeAI YouTube channel.

October

- [IDeAI Webinar Series started on 4th of October](#)
In 12 webinars the IDeAI researchers presented their main results via a web broadcast, which was freely accessible via the internet.
- [IDeAI Webinar series now on Youtube](#)
The IDeAI webinar series now has its own [YouTube channel](#) featuring the recordings of the past [webinars](#)! An overview over all currently uploaded videos can be found in the [IDeAI output section](#).





November

- [WBS Herbst Seminar](#)

The IDeAI hosted the WBS Herbst Seminar 2016 together with the WBS of the International Biometric Society to disseminate IDeAI results to academia and industry. The workshop took place at the Medical University of Vienna, Austria.

- [IDeAI Annual Meeting successful](#)

The IDeAI Annual Meeting took place in Vienna on November 7-8 at the Medical University of Vienna. Both research and dissemination strategies were refined for the final months together with the members of the External Advisory Board including representatives from patient organizations, academia, and regulatory offices. An additional highlight was Stephen Senn's dinner speech on the challenges of interdisciplinary collaboration.



2017

February

- [Rare Disease Day 2017](#)

The IDeAI consortium is proud to support the Rare Disease Day with new developments in statistical methodology for small populations.



March

- [Malta 2017: MMA-EURORDIS-COMP-IMI Conference](#)

Ralf-Dieter Hilgers presented IDeAl and its main results at the [MMA-EURORDIS-COMP-IMI Conference](#) in Malta. As an invited speaker, he seized the chance to present “[Innovative statistical design methodologies for clinical trials in small populations focussing on rare diseases](#)”.



- [Joint Dissemination Workshop at EMA](#)

The European Medicines Agency hosted a joint workshop of the three EU FP7 funded projects Asterix, IDeAl and InSPiRe on 29 & 30 March 2017 in London, UK.

April

- [Damian Brzyski earns distinguished paper award](#)

The Eastern North American Region (ENAR) of the International Biometric Society awarded Damian Brzyski with the Distinguished Student Paper Award for his work on group SLOPE which he performed within the IDeAl project. Brzyski’s paper, entitled “Group SLOPE as Method for SNPs Selection with the False Discovery Rate Control,” is focused on a new method for identifying groups of variables in a linear regression model that have an impact on the considered response.



New Results

Papers Published since January 2016

- Bird, S. M., Bailey, R. A., Grieve, A. P., Senn, S.: [Statistical issues in first-in-human studies on BIA 10-2474: Neglected comparison of protocol against practice.](#) Pharmaceutical Statistics 16 (2). March 2017.
- Senn, S.: [Letter to the Editor: Don't take it personally.](#) Significance 14 (1). February 2017.
- Hilgers, R.-D., König, F., Molenberghs, G., Senn, S.: [Design and analysis of clinical trials for small rare disease populations.](#) Journal of Rare Diseases Research & Treatment, 2016.
- Dosne, A.-G., Niebecker, R., Karlsson, M.O.: [IdOFV distributions: a new diagnostic for the adequacy of parameter uncertainty in nonlinear mixed-effects models applied to the bootstrap.](#) Journal of Pharmacokinetics and Pharmacodynamics 43 (6), 2016.
- Dosne, A.-G., Bergstrand, M., Harling, K., Karlsson, M.O.: [Improving the estimation of parameter uncertainty distributions in nonlinear mixed effects models using sampling importance resampling.](#) Journal of Pharmacokinetics and Pharmacodynamics 43 (6), 2016.
- Araujo, A., Julious, S., Senn, S.: [Understanding Variation in Sets of N-of-1 Trials.](#) PLoS ONE 11 (12), 2016.
- Ondra, T., Jobjörnsson, S., Beckman, R.A., Burman, C.-F., König, F., Stallard, N., Posch, M.: [Optimizing Trial Designs for Targeted Therapies.](#) PLoS ONE, 2016.
- Deng, C., Plan, E.L., Karlsson, M.O.: [Approaches for modeling within subject variability in pharmacometric count data analysis: dynamic inter-occasion variability and stochastic differential equations](#) Journal of Pharmacokinetics and Pharmacodynamics 43 (3), 2016.
- Reetz, K., Dogan, I., Hilgers, R.-D., Giunti, P., Mariotti, C., Durr, A., Boesch, S., Klopstock, T., Rodriguez de Rivera, F., Schöls, S., Klockgether, T., Bürk, K., Rai, M., Pandolfo, M., Schulz, J.: [Progression characteristics of the European Friedreich's Ataxia Consortium for Translational Studies \(EFACTS\): a 2 year cohort study](#), The Lancet Neurology. 2016.
- Eichler, H.-G., Bloechl-Daum, B., Bauer, P., Bretz, P., Brown, J., Hampson, L. V., Honig, P., Krams, M., Leufkens, H., Lim, R., Lumpkin, M. M., Murphy, M. J., Pignatti, F., Posch, M., Schneeweiss, S., Trusheim, M., König, F.: ['Threshold-crossing': A useful way to establish the counterfactual in clinical trials?](#) Clinical Pharmacology & Therapeutics. 2016.
- Van der Elst, W., Molenberghs, G., Hilgers, R.-D., Verbeke, G. and Heussen, N.: [Estimating the reliability of repeatedly measured endpoints based on linear mixed-effects models. A tutorial.](#) Pharmaceutical Statistics. 2016.
- Ueckert, S., Karlsson, M. and Hooker, A.: [Accelerating Monte Carlo power studies through parametric power estimation.](#) Journal of Pharmacokinetics and Pharmacodynamics Volume 43, Issue 2, pages 223-234, 2016.





- Gewandter, J., McDermott, M., McKeown, A., Hoang, K., Iwan, K., Kralovic, S., Rothstein, D., Gilron, I., Katz, N., Raja, S., Senn, S., Smith, S., Turk, D., Dworkin, R.: [Reporting of cross-over clinical trials of analgesic treatments for chronic pain: ACTTION systematic review and recommendations](#). PAIN 2016.
- Bauer, P. and König, F.: [Adaptive paediatric investigation plans, a small step to improve regulatory decision making in drug development for children](#). Pharmaceutical Statistics. 2016 July 12.
- Hilgers, R. D., Roes, K., and Stallard, N.: [Directions for new developments on statistical design and analysis of small population group trials](#). Orphanet Journal of Rare Diseases. 2016 June 14.
- Auffray, C., Balling, R., Barroso, I., Bencze, L., Benson, M., Bergeron, J., Bernal-Delgado, E., Blomberg, N., Bock, C., Conesa, A., Del Signore, S., Delogne, C., Devilee, P., Di Meglio, A., Eijkemans, R., Flicek, P., Graf, N., Grimm, V., Guchelaar, H.-j., Guo, Y., Glynne Gut, I., Hanbury, A., Hanif, S., Hilgers, R.-D., Honrado, A., Hose, D., Houwing-Duistermaat, Jeanine, Hubbard, T., Janacek, S. H., Karanikas, H., Kievits, T., Kohler, M., Kremer, A., Lanfear, J., Lengauer, T., Maes, E., Meert, T., Muller, W., Nickel, D., Oledzki, P., Pedersen, B., Petkovic, M., Pliakos, K., Rattray, M., Redon i Mas, J., Schneider, R., Sengstag, T., Serra Picamal, X., Spek, W., Tome, M., Vaas, L., van Batenburg, O., Vandelaer, M., Varnai, P., Volloslada, P., Vzacaino J. A., Wubbe, J., Zanetti, G.: [Making sense of big data in health research: Towards an European Union action plan](#). *Genome Medicine*. 2016.
- Lee, D. Brzyski, M. Bogdan: [Fast Saddle-Point Algorithm for Generalized Dantzig Selector and FDR Control with the Ordered l1-Norm](#). Proceedings of the 19th International Conference on Artificial Intelligence and Statistics, JMLR:W&CP vol.51, 780–789, 2016.
- Schorning, K., Bornkamp, B., Bretz, F. and Dette, H.: [Model Selection versus Model Averaging in Dose Finding Studies](#). Statistics in Medicine 2016.
- Riviere, M.-K., Ueckert S. and Mentré, F.: [A MCMC-method for the evaluation of the Fisher information matrix for nonlinear mixed effect models](#). Biostatistics 17. 2016.
- Bauer, P., Bretz, F., Dragalin, V., Koenig, F., and Wassmer, G.: [Authors' response to comments](#). Statistics in Medicine 35, 364-367. 2016.
- Bauer, P., Bretz, F., Dragalin, V., Koenig, F., and Wassmer, G.: [Twenty-five years of confirmatory adaptive designs: opportunities and pitfalls](#). Statistics in Medicine 35, 325-347. 2016
- Hlavin, G., Koenig, F., Male, C., Posch, M., and Bauer, P.: [Evidence, eminence and extrapolation](#). Statistics in Medicine. 2016.
- Magirr, D., Jaki, T., Koenig, F., and Posch, M., [Sample Size Reassessment and Hypothesis Testing in Adaptive Survival Trials](#). PLoS ONE. 11, e0146465. 2016.





- Alonso, A., Van der Elst W., Molenberghs, G., Buyse, M., and Burzykowski, T.: [An information-theoretic approach for the evaluation of surrogate endpoints based on causal inference](#). Biometrics 72, 2016.
- Rübber, A., Hilgers, R.-D., Leverkus, M.: [Hedgehog Blockade for Basal Cell Carcinoma. Coming at a \(Secondary Neoplastic\) Price](#). JAMA Dermatol. 2016.
- Van der Elst, W., Hermans, L., Verbeke, G., Kenward, M. G., Nassiri, V., & Molenberghs, G.: [Unbalanced cluster sizes and rates of convergence in mixed-effects models for clustered data](#). Journal of Statistical Computation and Stimulation, 2016.
- Jobjörnsson S, Forster M, Pertile P, Burman C-F.: [Late-Stage Pharmaceutical R&D for Rare Diseases under Two-Stage Regulation](#). University of York, Department of Economics and Related Studies, Discussion Paper 15/16.

To see further outputs such as presentations, short courses, videos or software programs visit the [output section at the IDEAL webpage](#):

<http://www.ideal.rwth-aachen.de>

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