



**IDeAI NEWSLETTER ISSUE 4**

**DECEMBER 2015**





## Impressum

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





## Editorial

The second project year was a very productive and successful – or in other word “ideal” year for the IDeAI-project.

First we passed the interim evaluation at the EU with flying colours motivating us continuing the successful path. Our publication record shows 12 papers in peer reviewed journal up to July, 5 out of 12 are in open access journals. Meanwhile another 5 paper are accepted for publication including a paper in the Annals of Statistics from Holger Dette's group. There are several papers submitted so that we can expect to end up with a rather impressive record.

The IDeAI-group was very active at conferences. One highlight was the DAE meeting at the Isaac Newton Institute in Cambridge in July 2015. Several IDeAI researchers, like Franz König, Holger Dette, Ralf-Dieter Hilgers, Andrew Hooker, France Mentrè, Marie-Karelle Riviere and Sebastian Ueckert were able to discuss their findings with members of the external advisory board like Rosemary Bailey, Bill Rosenberger, Chris Jennisson and Steven Julious as well as other world leading experts in design of clinical trials. The talks are video streamed and online available at the homepage of the Isaac Newton Institute ([www.newton.ac.uk](http://www.newton.ac.uk), links to all presentations can be found in the previous newsletter).

Moreover in August a huge group of IDeAI researchers were present at the ISCB 2015 in Utrecht. A workshop on randomization was held by Ralf-Dieter Hilgers (IDeAI) and Armin Koch (Asterix). Presentations of IDeAI results were given by Stephen Senn, Artur Araujo, Kathrin Möllenhoff, Marie-Karelle Riviere, Diane Uschner, David Schindler and Nicole Heussen.

In September Ralf-Dieter Hilgers, Franz König and Nicole Heussen represented the IDeAI project at the 9th International Conference on Multiple Comparison Procedures in Hyderabad, India. Intensive discussions with Martin Posch from the Asterix and the Inspire project as well as Andreas Faldum and Werner Brannath from the recently funded BMBF funded project “Adaptive designs in individualized therapy“ express the high level of scientific interchange with other research groups dealing with small clinical trials.

Starting with the special invited session about the methodologies in small clinical trials at the ISCB in Utrecht, where Ralf-Dieter Hilgers (IDeAI), Kit Roes (Asterix) and Nigel Stallard (Inspire) report about their projects, joint session were organised in October at the Annual Novartis Biostatistics Conference 2015 hosted by Novartis and at the MRC workshop on clinical trials in small populations hosted by the Royal Statistical Society in London in December. But, Dieter, Kit and Nigel were not only giving talks on their projects, they also plan to publish a joint paper on small population clinical trials, which should be submitted in the first half of 2016.

These are clear signs, that our project reaches increasing awareness, its developed methods are of interest and will be discussed by physicians. This is supported by a recently accepted Editorial in JAMA Dermatology (Leverkus, Hilgers, Rübber) where IDeAI methods are mentioned for further trials in the context of the rare disease “advanced basal cell carcinoma”. And recently, Ralf-Dieter Hilgers serves as biostatistical consultant for the European Friedreich's Ataxia Consortium for Translational Studies (EFacts, [www.e-facts.eu/](http://www.e-facts.eu/)) via his contact to Professor Jörg Schulz, Aachen University. Both designed a clinical trial for treatment of Friedreich's Ataxia which was submitted to the DFG (German Research Foundation).

So the way from bench (=development of statistical methods) to bedside (=application of methods in clinical trials) is paved and goes faster than expected. One striking example for the use of our work is the application of a method developed in WP10 to evaluate surrogacy in the setting where both the surrogate and true endpoint are binary in a real-life industry dataset from Johnson &





Johnson. One major challenge for the next year will be to bring our methods to the regulators during the IRDiRC task force meeting on Small Population Clinical Trials in the early March hosted by the EMA in London. But already this year there have been intensive interactions with regulatory authorities and industry. Christoph Male gave a presentation on the “extrapolation framework – status quo and issues to be resolved” at the [European Medicines Agency workshop](#) on extrapolation across age groups. Furthermore, there was also an IDeAI presentation on how to weigh the strength of prior information and clarify the expected level of evidence (based on the WP4 paper Evidence, Eminence and Extrapolation). Also earlier this year Peter Bauer, Franz Koenig and Martin Posch (Asterix, InSPiRE) gave an invited special training on “Trends in adaptive design and statistical approaches to small population group trials in EU” at the Japanese regulatory agency [PMDA](#).

I am deeply grateful for the work of my collaboration partners Franz König, Holger Dette, France Mentré, Stephen Senn, Mats Karlsson, Malagorzata Bogdan, Carl Fredrik Burman, Geert Molenberghs and Christoph Male and their co-workers and looking forward to a very productive 2016.

Dieter



Participants of the 2nd IDeAI Annual Meeting in Leuven (Belgium).



## Are you interested to learn more about our methods? Join our short courses!

One of our major objectives is to reach a broad audience in the clinical trials community, so that methods developed under the umbrella of the IDeAI project will eventually be taken up and change the landscape of clinical trials conducted in small populations such as in rare diseases, orphan drugs, paediatrics studies or in personalized medicine.

We offer tailored short courses and trainings both for statisticians or non-statisticians. We are flexible in organizing such training as stand-alone events or e.g., in the margins of a larger conference as pre- or post-conference course. Such tailored training session may be attractive for patient organizations, pharmaceutical companies, CROs, ethics committees, regulatory agencies, clinical trial investigators, statisticians, clinical trial expert in rare diseases, personalized medicines or paediatrics.

Topics may cover N-of-1 trials, cross-over designs, adaptive designs, randomisation, biomarkers, dose-finding, longitudinal data, missing data, pharmacometrics, meta-analysis.

If you are interested in having a tailored short course, workshop or specific training sessions on topics related to the research fields of our [workpackages](http://www.ideal.rwth-aachen.de/?page_id=58) (see [http://www.ideal.rwth-aachen.de/?page\\_id=58](http://www.ideal.rwth-aachen.de/?page_id=58)), please contact our coordinator Professor Ralf-Dieter Hilgers for further details [[rhilgers@ukaachen.de](mailto:rhilgers@ukaachen.de)]

In the following table a selection of short courses and workshops are listed that were held in the past:

| Title  | Presenter  | Date and Place   |
|--|--|--|
| <a href="#">Supporting the pathways to trials for rare diseases: Clinical trial design and other considerations. Part 1: Clinical trial designs for small population group trials.</a> | R.-D. Hilgers (WP 2)   | ECRD Invited Workshop. 2014 May 9. Berlin, Germany                                       |
| <a href="#">Adaptive Clinical Trial Designs.</a>   | F. König (WP 4), M. Posch, G. Wassmer  | Symposium on Small Populations. 2014 July 3. Vienna, Austria                             |
| <a href="#">Randomisation and Stratification in clinical trials</a>  | L. Aguirre Dávila, E. Budde, S. Ernst, T. Framke, A. Gonnermann, R.-D. Hilgers (WP 2), A. Koch, M. Kottas, D. Schindler (WP 2) , L. Spineli, D. Uschner (WP 2), K. Weber | Symposium on Small Populations. 2014 July 3. Vienna, Austria                             |
| <a href="#">Surrogate marker evaluation in clinical trials</a>   | W. van der Elst (WP 10)  | Symposium on Small Populations. 2014 July 3. Vienna, Austria                             |
| <a href="#">Adaptive Designs and Multiple Testing in Clinical Trials</a>   | F. König (WP 4), and M. Posch  | Summer school at the Universtat Politécnica de Catalunya. 2014 July 8-10. Bcelona, Spain |





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| Novel approaches to multiple test problems, with applications to adaptive designs and dose finding | F. König (WP 4)  | ISCB Short Course<br>27-28 November 2014.<br>Budapest, Hungary   |
| <a href="#"><u>Stratification and randomization in clinical trials</u></a>                         | R.-D. Hilgers, D. Uschner and D. Schindler (all WP 2) in collaboration with Armin Koch | ISCB Workshop<br>2015 August 23.<br>Utrecht, Netherlands   |
| <a href="#"><u>Cross-over trial in clinical research</u></a>                                       | Stephen Senn (WP 6)  | PSI Training Course<br>2015 March 4.<br>Heathrow, UK   |
| Longitudinal and Incomplete Data   | Geert Verbeke & Geert Molenberghs (WP 10)  | Short Course at the IDEAL annual meeting, 2015<br>November 4. Leuven, Belgium                            |
| Covariate model building in non-linear mixed effects models  | Mats Karlsson  | Uppsala Pharmacometrics Summer School<br>2015 August 10-14.  |
| Pharmacokinetic/pharmacodynamics modelling   | Mats Karlsson  | Uppsala Pharmacometrics Summer School<br>2015 August 17-21   |
| Model building and diagnostics for nonlinear mixed effects models                                  | Mats Karlsson  | US Food & Drug Administration<br>2015 October 6-8;<br><br>A European Regulatory Course<br>2016 March 2-4 |

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## Latest IDeAI News posted on the website

- [Gerald Hlavin receives Arthur Linder Award](#)
  - The Austro-Swiss Section of the International Biometrical Association honoured Gerald Hlavin for his work “Evidence, Eminence and Extrapolation” with the Arthur Linder Award.
- [IDeAI researchers disseminate latest findings at ISCB 2015](#)
  - Several researchers of the IDeAI project were meeting at ISCB 2015 in Utrecht in order to disseminate their latest findings on methodology for small population group trials.
- [IDeAI researchers discuss frontiers of confirmatory inference in small populations at MCP 2015](#)
  - The IDeAI project is strongly represented to discuss multiplicity issues related to rare diseases at the [9th International Conference on Multiple Comparison Procedures MCP2015](#), September 2nd – 5th, in Hyderabad, India

## New Results

### Articles accepted in peer-reviewed journals

- Bogdan, M., van den Berg, E., Sabatti, C., Su, W., Candes, E. J. "SLOPE - Adaptive Variable Selection via Convex Optimization." *Annals of Applied Statistics*, 9 (3), 1103--1140, 2015.
- Dette, Holger, and Schorning, Kirsten. "Optimal designs for comparing curves." *Annals of Statistics* (2016)
- Hlavin, G., Koenig, F., Male, C., Posch, M., and Bauer, P. "Evidence, Eminence and Extrapolation." *Statistics in Medicine* (2016)
- Van der Elst, Wim, Molenberghs, Geert, and Alonso, Ariel. "Exploring the relationship between the causal-inference and meta-analytic paradigms for the evaluation of surrogate endpoints." *Statistics in Medicine* (2015)
- 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 Simulation* (2015)





## Presentations

- “A causal-inference approach for the validation of binary surrogate and true endpoints based on information-theory”. W. Van der Elst, A. Alonso. 2015 Apr 26. Maastricht University and Janssen Pharmaceutica, Maastricht, Netherlands.
- „Adaptive graph-based multiple testing procedure” (invited). F. Koenig, F. Klingmueller, M. Posch. 2015 May 21. PSI Pharmaceutical Statistics & RSS Journal Club Webinar on Adaptive Designs.
- “Clusters With Random Size: Maximum Likelihood: Weighted Split-Sample Pseudo-likelihood”. G. Molenberghs. 2015 Jun 05. (IB)2, ULB-VUB, Brussels, Belgium.
- “Pseudo-likelihood and Split-sample Methods in Small Populations / Small Trials”. G. Molenberghs. 2015 Jun 11. Small Clinical Trials, Biltsche Hoek, Netherlands.
- “Confirmatory adaptive designs using closed-test MCP-Mod” (invited). F. Koenig. 2015 Jun 27 - Jul 1. ISBS-DIA Joint Symposium on Biopharmaceutical Statistics. Beijing, China.
- [“Confirmatory Testing for a Beneficial Treatment Effect in Dose-Response Studies using MCP-Mod and an Adaptive Interim Analysis”](#) (invited). F. Koenig. 2015 Jul 9. Design of Experiments in Drug Development. Isaac Newton Institute, Cambridge, UK.
- [“Efficient tests for the similarity of dose response curves”](#). K. Möllenhoff. 2015 Aug 24. ISCB Utrecht 2015, Utrecht, Netherlands.
- “Strategies for dealing with missing data in randomization tests”. N. Heussen. 2015 Aug 24. ISCB 2015, Utrecht, Netherlands.
- [“Understanding variation in n-of-1 trials”](#) A. Araujo. 2015 Aug 24. ISCB 2015, Utrecht, Netherlands.
- “New developments in integrated design and analysis of small population group trials (IDeAI)” (invited). R.-D. Hilgers. 2015 Aug 24. ISCB 2015, Utrecht, Netherlands.
- “Baselines as possible controls in trials in small populations”. S. Senn. 2015 Aug 24. ISCB 2015, Utrecht, Netherlands.
- [“The effect of selection bias on the test decision of the randomization test in small population group trials”](#). D. Uschner. 2015 Aug 24. ISCB 2015, Utrecht, Netherlands.
- [“Desirability of restricted randomization procedures in small population group trials in case of selection and chronological bias”](#). D. Schindler. 2015 Aug 24. ISCB 2015, Utrecht, Netherlands.
- [“Evaluation of the fisher information matrix without linearization, in nonlinear mixed effect models for discrete and continuous outcomes”](#). M.K. Riviere. 2015 Aug 24. ISCB 2015, Utrecht, Netherlands.







- “The selection of relevant groups of explanatory variables in GWA studies”. D. Brzyski. 2015 Aug 31. 19th European Young Statisticians Meeting, Prague, Czech Republic.
- “Genome Wide Association Studies with Sorted L-one Penalized Estimation (SLOPE)” (invited). M. Bogdan. 2015 Sep 03. International Conference on Operations Research, Vienna, Austria.
- Strategies for Dealing with Missing Values in Randomization Tests Under Different Randomization Procedures, Nicole Heussen. 2015 September 3. MCP, Hyderabad.
- A Unified Criterion for Assessing the Biased Test Decision in Cases of Selection and Chronological Bias. Ralf-Dieter Hilgers. 2015 September 3. MCP, Hyderabad.
- „Two-Step Procedures Using Safety for Multiplicity Adjustments in Many-One Tests” (invited). F. Koenig, G. Hlavin, P. Bauer. 2015 Sep 2-5. 9th International Conference on Multiple Comparison Procedures in Hyderabad, India.
- [“Selecting an appropriate randomization procedure for a small population group trial on the basis of a linked optimization criterion”](#). D. Schindler, R.D. Hilgers. 2015 Sep 24. Eighth International Workshop on Simulation, Vienna, Austria.
- [“A software tool for the design and analysis of small population group trials”](#). D. Uschner, D. Schindler, R.D. Hilgers. 2015 Sep 24. Eighth International Workshop on Simulation, Vienna, Austria.
- “Evidence, Eminence and Extrapolation”. G. Hlavin. 2015 Sep 24. Eighth International Workshop on Simulation, Vienna, Austria.
- “Dimension reduction with partially integrated penalized likelihood”. P. Sobczyk. 2015 Sep 24. Eighth International Workshop on Simulation, Vienna, Austria.
- “SLOPE - Adaptive Variable Selection via Convex Optimization” (invited). M. Bogdan. 2015 Sep 25. Eighth International Workshop on Simulation, Vienna, Austria.
- “Adaptive designs for confirmatory model based decisions using MCP-Mod”. S. Krasnozhon. 2015 Sep 21-25. Eighth International Workshop on Simulation, Vienna, Austria.
- “New developments in the design and analysis of small population group trials” (invited). R.-D. Hilgers. 2015 Oct 12. Annual Novartis Biostatistics Conference, Basel, Switzerland.
- [“How to use randomizeR to investigate randomization tests in the presence of selection bias”](#) (invited). D. Uschner. 2015 Oct 16. Statistics Seminar Series, George Mason University, Fairfax, Virginia, USA.
- “Evidence, Eminence and Extrapolation”. G. Hlavin. 2015 Oct 17. 20th Young Statisticians Meeting, Vienna, Austria.





- “Selecting explanatory variables with SLOPE” (invited). M. Bogdan. 2015 Oct 23. Departmental Biostatistics Seminar, Fairbanks School of Public Health of Indiana University, Indianapolis, USA.
- “[randomizeR – An R-package that implements randomization and considers biases](#)”. D. Uschner. 2015 Oct 28. National Institute of Health, Rockville, Maryland, USA.
- “The Crisis of Reproducibility: P-Values are not the Problem” (invited). S. Senn. 2015 Nov 23. Novartis. Basel, Switzerland.
- “Clinical Trials are not enough” (invited). S. Senn. 2015 Nov 23. Novartis. Basel, Switzerland.
- “The Crisis of Reproducibility: P-Values are not the Problem” (invited). S. Senn. 2015 Nov 24. EBPI Colloquia, University of Zurich. Zurich, Switzerland.
- “[Integrated Design and Analysis of Clinical Trials in Small Population Groups \(The IDeA Project\)](#)” (invited). R.D. Hilgers. 2015 Nov 30. Clinical Trials in Small Populations Workshop, University of Lancaster, Lecture Theatre, Royal Statistical Society, London, UK.
- “False discoveries occur early on the LASSO path” (invited). M. Bogdan. 2015 Dec 12. CMStatistics, London, UK.
- “Adaptive selection via SLOPE” (invited). D. Brzyski. 2015 Dec 13. CMStatistics, London, UK.
- “P Values and replication: the problem is not what you think” (invited). S. Senn. 2015 Dec 16. Wednesday Lunch Time Seminar Series, MRC Cognition and Brain Sciences Unit, University of Cambridge, Cambridge, UK.
- “Take it to the limit: quantitation, likelihood, modelling, inference and other matters” (invited). S. Senn. 2015 Dec 17. Pharmacology 2015, London, UK.

### Conference Posters

- “Split-sample Based and Multiple Imputation Estimation & Computation for Data Hierarchies (Meta-analysis, Clinical Trials, and Beyond)” (invited poster). G. Molenberghs. 2015 Mar 15. Spring Meeting of the Eastern North American Region, Miami, Florida).





## Short Courses and Workshops

- “Rare diseases: aspects related to the design of the study and the statistical analysis of data”. L. Bruckers, W. Van der Elst, V. Nassiri, G. Molenberghs. 2015 Dec 03. Workshop in ‘The Rare Disease Fibrodysplasia Ossificans Progressiva’ conference, Leiden, Netherlands.
- „[Trends in adaptive design and statistical approaches to small population group trials in EU](#)”, P. Bauer, F. König, and M. Posch. 2015 Mar 27. PMDA – Pharmaceuticals and Medical Devices Agency. Tokyo, Japan.

## Panel Discussions

- Frontiers of Confirmatory Inference in Small Populations (Panel Session. Organizers: Franz Koenig and Martin Posch) with talks of Ralf-Dieter Hilgers: Some Aspects of Clinical Trials in Small Population Groups and Carl-Fredrik Burman: Science, Logic and Patients. On Inference in Small Disease Populations and a Panel Discussion with: John Scott, Ralf-Dieter Hilgers, Lisa Hampson, Carl-Fredrik Burman and Andreas Faldum. 2015 September 4. MCP, Hyderabad.
- Regulatory Panel Discussion. F. Koenig (panelist). 2015 Jun 27- Jul 1. ISBS-DIA Joint Symposium on Biopharmaceutical Statistics. Beijing, China.

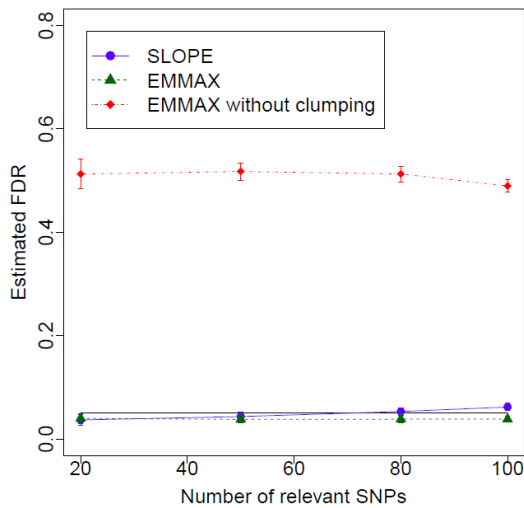
## Statistical Software

- R Package ‘[TestingSimilarity](#)’ (Kathrin Moellenhoff): Bootstrap Test for Similarity of Dose Response Curves Concerning the Maximum Absolute Deviation.
  - This package provides a bootstrap test which decides whether two dose response curves can be assumed as equal concerning their maximum absolute deviation.
- R Package ‘[EffectTreat](#)’ (W. Van der Elst, A. Alonso & G. Molenberghs): Prediction of Therapeutic Success.
  - This package allows for the quantification of the predictive causal association (i.e., the association between the predictor variable and the individual causal effect of the treatment) and related metrics.
- R package ‘[CorrMixed](#)’ (W. Van der Elst, G. Molenberghs, D. Hilgers, & N. Heussen): Estimate Correlations Between Repeatedly Measured Endpoints (e.g., Reliability) Based on Linear Mixed-Effects Models
  - This package allows for estimating these correlations based on mixed-effects models.

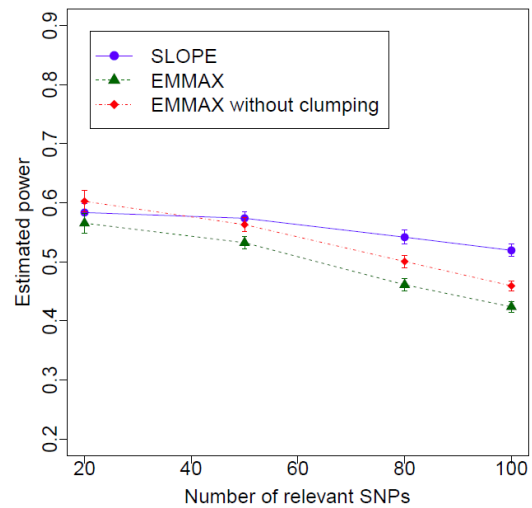




- R package '[geneSLOPE](#)' (P. Sobczyk [Package Maintainer]): Genome Wide Association Studies with SLOPE.
  - Reference: Brzyski, D., Peterson, C., Sobczyk, P., Bogdan, M., Sabatti, C. "GeneSLOPE - Convex optimization for GWAS with FDR control." (in preparation).
  - See also the figure below.



(a) FDR



(b) Power

**Comparison between SLOPE and EMMAX (applied together with the Benjamini - Hochberg procedure (B-H)) for four levels of sparsity,  $K=\{20; 50; 80; 100\}$ . Clumping with  $\rho = 0.3$  was used with SLOPE and EMMAX. Additionally, EMMAX without clumping was considered, where B-H was applied directly to p-values given by EMMAX. Simulations were performed with the real genotype data and level 0.05 was defined as target FDR.**

- R package '[MIXFIM](#)' (M.-K. Riviere-Jourdan & F. Mentre): Evaluation of the FIM in NLMEMs using MCMC
  - Evaluation and optimization of the Fisher Information Matrix in NonLinear Mixed Effect Models using Markov Chains Monte Carlo for continuous and discrete data.





## Abstracts of Articles in Peer-Reviewed Journals

Bogdan, M., van den Berg, E., Sabatti, C., Su, W., Candes, E. J. "SLOPE - Adaptive Variable Selection via Convex Optimization." *Annals of Applied Statistics* (2015)

We introduce a new estimator for the vector of regression coefficients in the multiple regression model. SLOPE, short for Sorted L-One Penalized Estimation, is the solution to the convex program and we demonstrate a solution algorithm whose computational complexity is roughly comparable to the computational complexity of LASSO. Here, the regularizer is a sorted  $L_1$  norm, which penalizes the regression coefficients according to their rank: the higher the rank - i.e. the stronger the signal - the larger the penalty. This is similar to the famous Benjamini-Hochberg procedure for multiple testing, which compares more significant p-values with more stringent thresholds. SLOPE aims to provide finite sample guarantees on the selected model; of special interest is the false discovery rate (FDR), defined as the expected proportion of irrelevant regressors among all selected predictors. Under orthogonal designs, we provide the sequence of tuning parameters for SLOPE, which provably controls FDR. Moreover, our simulation studies and the analysis of real genetic data show that SLOPE has appreciable inferential properties under more general designs.

Dette, H., Schorning, K. "Optimal designs for comparing curves." *Annals of Statistics* (2016)

We consider the optimal design problem for a comparison of two regression curves, which is used to establish the similarity between the dose response relationships of two groups. An optimal pair of designs minimizes the width of the confidence band for the difference between the two regression functions. Optimal design theory (equivalence theorems, efficiency bounds) is developed for this non standard design problem and for some commonly used dose response models optimal designs are found explicitly. The results are illustrated in several examples modeling dose response relationships. It is demonstrated that the optimal pair of designs for the comparison of the regression curves is **not** the pair of the optimal designs for the individual models. In particular it is shown that the use of the optimal designs proposed in this paper instead of commonly used "non-optimal" designs yields a reduction of the width of the confidence band by more than 50%.

Hlavin, G., Koenig, F., Male, C., Posch, M., and Bauer, P. "Evidence, Eminence and Extrapolation." *Statistics in Medicine* (2016)

A full independent drug development programme to demonstrate efficacy may not be ethical and/or feasible in small populations such as paediatric populations or orphan indications. Different levels of extrapolation from a larger population to smaller target populations are widely used for supporting decisions in this situation. There are guidance documents in drug regulation, where a weakening of the statistical rigour for trials in the target population is mentioned to be an option for dealing with this problem. To this end we propose clinical trials designs, which make use of prior knowledge on efficacy for inference. We formulate a framework based on prior beliefs in order to investigate when the significance level for the test of the primary endpoint in confirmatory trials can be relaxed (and thus the sample size can be reduced) in the target population while controlling a certain posterior belief in effectiveness after rejection of the null hypothesis in the corresponding confirmatory statistical test. We show that point-priors may be used in the argumentation since under certain constraints they have favourable limiting properties among other types of priors. The crucial quantity to be elicited is the prior belief in the possibility of extrapolation from a larger population to the target population. We try to illustrate an existing decision tree for extrapolation to paediatric populations within our framework.





Van der Elst, W., Molenberghs, G., and Alonso A. "Exploring the relationship between the causal-inference and meta-analytic paradigms for the evaluation of surrogate endpoints." *Statistics in Medicine* (2015)

Nowadays, two main frameworks for the evaluation of surrogate endpoints, based on causal-inference and meta-analysis, dominate the scene. Earlier work showed that the metrics of surrogacy introduced in both paradigms are related, although in a complex way that is difficult to study analytically. In the present work, this relationship is further examined using simulations and the analysis of a case study. The results indicate that the extent to which both paradigms lead to similar conclusions regarding the validity of the surrogate, depends on a complex interplay between multiple factors like the ratio of the between and within trial variability and the unidentifiable correlations between the potential outcomes. All the analyses were carried out using the newly developed R package *Surrogate*, which is freely available via CRAN.

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 Simulation* (2015)

Convergence problems often arise when complex linear mixed-effects models are fitted. Previous simulation studies (see, e.g. [Buyse M, Molenberghs G, Burzykowski T, Renard D, Geys H. The validation of surrogate endpoints in meta-analyses of randomized experiments. *Biostatistics*. 2000;1:49–67, Renard D, Geys H, Molenberghs G, Burzykowski T, Buyse M. Validation of surrogate endpoints in multiple randomized clinical trials with discrete outcomes. *Biom J*. 2002;44:921–935]) have shown that model convergence rates were higher (i) when the number of available clusters in the data increased, and (ii) when the size of the between-cluster variability increased (relative to the size of the residual variability). The aim of the present simulation study is to further extend these findings by examining the effect of an additional factor that is hypothesized to affect model convergence, i.e. imbalance in cluster size. The results showed that divergence rates were substantially higher for data sets with unbalanced cluster sizes – in particular when the model at hand had a complex hierarchical structure. Furthermore, the use of multiple imputation to restore 'balance' in unbalanced data sets reduces model convergence problems.

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





**WE WISH YOU**

**A MERRY CHRISTMAS**

**&**

**A HAPPY NEW YEAR 2016!**

