IDeAl NEWSLETTER ISSUE 2

DECEMBER 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

The first project year of the IDeAl consortium appears to be a very productive time. Within all work packages new methodologies, which are useful for establishing efficacy and safety in small population trials were developed or evaluated. The details for particular research findings are given in this and the preceding newsletter and found their way to the scientific community by 8 published papers, further papers have already been submitted. Further the consortium presented research at various occasions, including invitations to the ECRD, the Clinical Trials´ Day of the European Clinical Research Infrastructures Network, the ISCB 2014, the symposium on Small Populations in Vienna, EMA workshop on subgroups, and the FDA & SCT workshop.

To be more specific, the consortium trod the path to the rare disease community at the 7th European Congress on Rare Disease in Berlin in May this year. At the poster presentation various representatives of patient advocacy groups and researcher were informed about the development program of IDeAl. Preceding the conference Ralf-Dieter Hilgers gave a workshop on clinical trial design for small sample population groups embedded in the tutorial on supporting the pathway to trials for rare diseases together with the TACT group (http://www.treat-nmd.eu/resources/tact/committee-members/). Three other workshops about randomization (joint with Armin Kochs group from the ASTERIX project), Adaptive Designs (F. König & Gernot Wassmer, joint work with Martin Posch from InSPIRE and Asterix project) and Surrogate marker (W. van der Elst, IDeAl) were successfully conducted at the Vienna symposium on Small Population group trials in July 2014 with about 30 to 40 participants each.

Other workshops were given in Barcelona, Budapest including topics as adaptive designs and multiplicity, given by Franz König and Frank Bretz. Also a seminar was given in Exeter by Stephen Senn, dealing with personalized medicine.

A highlight during the year was the joint workshop on Small Population Group Trials of the three EU funded projects ASTERIX, IDEAL and Inspire in July this year in Vienna. Here various stakeholders, regulators, patient advocacy groups and academia met to discuss and share their point of view. The expectations of the EU was given by the EU project officer Diane Salmone.

The Scientific Advisory Board met the day before the symposium and later in November during the Paris annual meeting. Odile Kremp moved to the ministery of health in France, and was substituted by Ségolène Aymé as a representative of the ORPHANET, bringing among others the perspectives of IRIDIC, Orphanet and the WHO into the IDeAl consortium. Bill Rosenberger spent nearly 4 month of his sabbatical as Fullbright fellow at the Department of Medical Statistics, RTWH Aachen University. During this stay he as a member of the external Advisory Board took the opportunity to get in touch with various research groups of the IDeAl project and thus stimulating joint research. The young scientist, the group of research assistants working within the project met two times to share their knowledge and stimulate joint work at the symposium in Vienna and the annual meeting in Paris.

And finally scientific comments to three EMA guidelines „Draft Guideline on the investigation of subgroups in confirmatory clinical trials (EMA/539146/2013)", 'Draft guideline on adjustment for baseline covariates' (EMA/295050/2013) and '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) related to the design and analysis of small population clinical trials were submitted by the IDeAl group. The consortium represented by Geert Molenberghs and Ralf-Dieter Hilgers was invited to present and chair there point of view with a large number of people from academia, industry and regulator during the one day EMA workshop on November 7th in London.

So I am looking back to a very productive first year with a challenging outlook to important events in the next year under involvement of the IDeAl consortium. Several meetings are already planned where members of the group will participate and extend their research findings. Among others are a special day on small population group trials during the DAE meeting at the Isaac Netwon Institute in Cambridge in July, a special joint session at the ISCB in Utrecht in August next year, a special session on small population groups trials during the 8th International Workshop on Simulation in Vienna. Further occasions to meet and discuss topics on small population group trials are mentioned in this newsletter.
I am looking forward to our development which might change various aspects of small population group trials.

Ralf Dieter Hilgers, Coordinator of the IDeAl Project

Research Areas of our Scientific Work Packages (WP)

- **WP2: Assessment of randomisation procedures and randomisation based tests in small population groups**

  In this work package randomization procedures that satisfy certain criteria are being investigated. Here the focus lies on procedures that control for certain types of biases (selection bias and time trend). Different kinds of procedures are included. In the course of the research, an R package is being developed which is directed to biostatisticians to provide tools for experimental design.

- **WP3: Extrapolating dose-response information to small population groups**

  In this work package, the equivalence of two dose response curves is being investigated, and highly accurate confident bands are being developed. It was possible to achieve a gain in accuracy of the confidence bands while reducing the computational effort. Furthermore, a test for the similarity of dose response curves has been developed.

- **WP4: Adaptive design studies in small population groups**

  In this work package the application of adaptive designs in small populations is investigated. What is the impact of performing adaptation on the operating characteristics of clinical trial designs? This includes research on confirmatory dose finding studies and incorporating external knowledge to tackle research questions in small populations efficiently. The latter provides an innovative Bayesian model for the extrapolation of evidence from source population (e.g. adults) to the target population (e.g. children) which incorporates the scepticism for the possibility of extrapolation. For confirmatory dose finding studies the MCPMod approach, which was recently qualified by the European Medicines Agency, has been extended allowing the testing of individual doses and design modifications at an interim.

- **WP5: Optimal design in mixed models to analyse studies in small population groups**

  Until now, the research in this work package can be divided in two main parts. In the first part, the approaches MC simulation and Gaussian quadrature were used for the efficient calculation of the Fisher information matrix for discrete mixed models, avoiding linearization. In the second part, adaptive designs for PKPD Models in Oncology were investigated. Several designs were evaluated in a simulation study, leading to recommendations to two-stage adaptive designs.

- **WP6: Design of pharmacogenetic small population group trials including cross-over trials, n-of-1 trials and enrichment trials**

  Four main topics are currently being investigated. First, a literature research on N-of-1-trials is nearly complete and suggested approaches to analysis are being prepared with example programs in R and SAS. Second, the research on the use of baselines while making assumptions about trends has shown to what degree the precision for the estimate a treatment effect can be increased. Third, it was shown that the problem that covariate-adjustment in small samples may not permit the gains possible in large samples can be addressed by using external information based on previous analogous trials. Fourth, research showed that, provided that fixed-effects weighting is used, meta-analysts do not need to take account of sequential stopping rules used in individual trials.

- **WP7: Simulation of clinical trials in small population groups**

  The main aim of the research in WP7 is to show whether NLME can offer an advantage to planned analysis design. The new approaches can decrease the sample size substantially. E.g. the Parametric Power Estimation Algorithm makes a real effect on study length and number of subjects while reducing the computational effort substantially in comparison with the regular Monte Carlo Method. Several innovative methods are already being investigated in this research, including randomization tests, bootstrapping, importance weighting and SIR. Generalizations are possible.

- **WP8: Genetic factors influencing the response to the therapy in small population group trials**

  The research in this work package can be divided into two main parts: The identification of genetic pathways and the identification of regulatory elements. In the first part, the goal is to find the major regulatory process and identify the genes that are the triggers behind the whole group. Subspace clustering is being developed to achieve this aim, and the algorithm for finding the solutions is being implemented in an R package. In the second part, the aim is to find the location of the genome with some gene expression. The multiple testing problems arising in this research are tackled with model selection tools and innovative methods like heuristic evaluation criteria.

- **WP9: Decision analysis in small population groups**

  Before conducting a clinical trial, the experimenters should ask themselves a number of questions: “Should we even do the trial? Should we even develop the drug?” The good thing about small population groups is that we can develop new methods. Regulators are more aware that new approaches are necessary. Some innovation can maybe be carried over to larger populations. The decision analysis on the drugs could influence how many and what drugs get released to patients. The research in this WP incorporates these considerations.

- **WP10: Biomarker surrogate endpoints in small population groups**

  In the models for surrogate endpoints, non-convergence is often a problem. Balance is a relevant factor for convergence. This issue is being investigated extensively, from both a theoretical standpoint as well as using simulations. It follows that both multiple imputation and pseudo-likelihood methodology is extremely helpful in drastically enhancing computational ease, whilst leading to no or at most minimal loss of efficiency. The results have already been applied in real life situations. The results are relevant for (small and large) meta-analytic and other hierarchical studies.

- **WP11: Dissemination**

  The most exiting results are the joint activities with the DIA working group on small populations, the presence in social media networks, the IDeAl website, and the bi-annual newsletter. A joint symposium on small populations was organized together with the FP7 projects Asterix and Inspire in July. In December a joint seminar was organized with the WBS section of the International Biometric Society presenting the IDeAl results of various work packages (for the IDeAl presentations see section presentations). Furthermore, input to three regulatory guidelines has been given and the IDeAl point of view was communicated at various conferences, workshops and panel discussions.

News from the EAB

Three topics of importance to the project were presented by members of the External Advisory Board in the course of the 1st annual meeting taking place in Paris on November 3-4 2014:

Gerard Pons

"Innovative methodological approaches to facilitate the evaluation of medicinal products in children: strategy, methodology, tools"

Information from adults cannot simply be extrapolated to children. The highest priority is the protection of children. This leads to the trade-off of protecting children too much on the expense of not making any studies in children. A possible solution is to use more advanced statistical techniques. E.g. the effect of maturation on the PK-PD relationship is still not fully known, and a Bayesian approach can help overcome problems of narrow dose range in dose-finding studies in children. Still, the objective is not to develop the methodology but to protect young children with the methodology.

W.F. Rosenberger

"Issues in the design and analysis of rare disease clinical trials"

Rare diseases pose special problems for the statistical analysis. These problems should influence the design considerations. For example, the long recruitment phase in rare diseases might lead to a time trend in the data, which should be accounted for at design stage. Furthermore, predictability of future allocations is an issue in SPG and that allocation concealment and masking is not sufficient. However, predictability and balance are competing interests in SPG. Some of the problems could be mitigated if randomization was used as a basis for inference. As a consequence, it is recommended to use the inference technique that suits the problems best.

M. Forster

"Bayesian sequential experimentation and rare diseases: the effect of population size on expected time to a decision"

Orphan drugs are interesting from the point of health economy. One issue is that reimbursement does not follow from orphan status. For the development of our results, we need to look at costs and benefits. Varying the population which would benefit from the medical product might make a change. Another important consideration is the optimal stopping time for the trial. We literally need to think things from the back and compare the value of stopping with the value of continuing the trial. These results have a high impact in SPG.

IDeAl News posted on the webpage September 2014 until December 2014

October 2014

- William F. Rosenberger guest professor at UKA
  - He gave advice to the researchers in WP 2, and welcomed the opportunity of exchange with other EAB members and project partners.
- Course on Cross-Over Trials in Clinical Research
  - Two-day Course on Cross-Over Trials in Clinical Research at the WTCRF in Edinburgh held by Stephen Senn.

November 2014

- IDeAl Annual Meeting 2014
  - November 3-4, 2014; Paris
  - General Assembly, Annual Scientific Meeting and Young Scientist Meeting
- Young Scientist Meeting in Paris successfull
  - Topic: “Improve the cooperation between the partners”
- WBS-Winterseminar „Innovative Statistical Approaches in Drug Development“
  - December 2, 2014
  - Talks by RD Hilgers, Stephen Senn, Sergii Krasnozhon William F. Rosenberger, Holger Dette, Gerald Hlavin
- Statistics for Rare Diseases at ISCB 2015 (More details see section conferences)

December 2014

- R package for dimension reduction of genetic information now available online.
  - Package *varclust*
  - Released by Piotr Sobczyk
- Franz König was invited panelist in panel session at FDA & SCT/ QSPI workshop “Innovations in the Science and Practice of Clinical Trials”
  - Topic of the Discussion: “Rare Diseases / Small Trials & Rare Events / Large Trials”
  - December 8 & 9, 2014, Washington (program)
- IDeAl explicitly mentioned in recent methodology paper
  - *Methodology of clinical trials for rare diseases*
    Smith, C. T., Williamson, P. R., & Beresford, M. W. (2014). *Best Practice & Research Clinical Rheumatology*, *28*(2), 247-262.

New Results

Articles in peer-reviewed journals

- Tamm, M., and R-D. Hilgers. "Chronological Bias in Randomized Clinical Trials Arising from Different Types of Unobserved Time Trends." Methods Inf Med 53 (2014): 501-510. (now published)
- Graf, Alexandra C., Martin Posch, and Franz Koenig. "Adaptive designs for subpopulation analysis optimizing utility functions." Biometrical Journal (2014).
- Klinglmueller, Florian, Martin Posch, and Franz Koenig. "Adaptive graph-based multiple testing procedures." Pharmaceutical statistics 13.6 (2014): 345-356.

Presentations

- Presentations at the WBS Seminar. December 2, 2014. Vienna, Austria:
    - *"Some Aspects of Clinical Trials in Small Population Groups with Special Interest in Randomization"* - RD Hilgers
    - *"Seven myths of randomization"* - Stephen Senn
    - *"Adaptive designs for confirmatory model based decisions using MCP-Mod"* - Sergii Krasnozhon
    - *"Bayesian Dose-Finding Procedure Based on Compound Information and Ethical Criteria"* - William F. Rosenberger
    - *"Statistical inference for comparing dose-response curves"* - Holger Dette
    - *„Adapted levels of Evidence for small populations"* - Gerald Hlavin

- Mastering variation: Variance components and personalised medicine. S.Senn. October 24, 2014. ExIStA Seminar. University of Exeter, UK.
- Variabilty in Drug Response. S. Senn. Defining Drug Response for Stratified Medicine. 2014 October 23. UK Pharmacologenetics and Stratified Medicine Network. University of Liverpool in London, UK.
- Big thunder, little rain? F. König. Invited Talk. 2014 Nov 13. Joint BBS-EFSPI Seminar Data Sharing in Clinical Development. Basel, Switzerland.
- **Chronological bias caused by unobserved time trends in randomized clinical trials**. M. Tamm. 11 Oct 2014. AISC Greensboro, North Carolina, USA.
- Subgroup analysis: trying to get more from less? S. Senn, G. Molenbergh (Presenter), F. Koenig, R.-D. Hilgers. IDeAl presentation at European Medicines Agency workshop on the investigation of subgroups in confirmatory clinical trials. 2014 Nov 07. London, UK.

Short Courses

- ISCB Short Course in "**Novel approaches to multiple test problems, with applications to adaptive designs and dose finding**". F. König and F. Bretz. 27-28 November 2014. Budapest, Hungary.
- Cross-Over Trials in Clinical Research. S. Senn. November 17-18, 2014. Edinburgh, UK.

Conferences

- WBS-Winterseminar on Innovative Statistical Approaches in Drug Development.
    - December 2, 2014
    - Slides will be made available at http://www.meduniwien.ac.at/wbs/seminar.html

Statistical Software Programs

- R package for dimensionality reduction via variables clustering. P. Sobczyk [published 2014-12-06]

Upcoming IDeAl Events

- February 28, 2015; Rare Disease Day; http://www.rarediseaseday.org/
- June 15 – 19, 2015; ROeS - http://www.ibs-roes.org/iroes-2015/; University of Milano-Bicocca, Italy
    - Stephen Senn gives a presentation in invited session “Does size really not matter? Evaluation of treatment effects in subgroups and other small populations” organized by F. Koenig and M. Posch.
- July 06 – 10, 2015; Design and Analysis of Experiments in Healthcare; Isaac Newton Institute, Cambridge, UK
- August 23 – 27, 2015; ISCB; http://www.iscb2015.info/; Utrecht, Netherlands
    - Invited presentation in session “Statistical methodology for clinical research in rare diseases”, RD Hilgers
    - Invited short course on “Randomisation and stratification in clinical trials”, RD Hilgers

- 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 2015; Next Annual Meeting of the whole IDeAl consortium; Hasselt, Belgium

Abstracts of Articles in Peer-Reviewed Journals

Graf, Alexandra C., Peter Bauer, Ekkehard Glimm, and Franz Koenig. "Maximum type 1 error rate inflation in multiarmed clinical trials with adaptive interim sample size modifications." Biometrical Journal (2014).

Sample size modifications in the interim analyses of an adaptive design can inflate the type 1 error rate, if test statistics and critical boundaries are used in the final analysis as if no modification had been made. While this is already true for designs with an overall change of the sample size in a balanced treatment-control comparison, the inflation can be much larger if in addition a modification of allocation ratios is allowed as well. In this paper, we investigate adaptive designs with several treatment arms compared to a single common control group. Regarding modifications, we consider treatment arm selection as well as modifications of overall sample size and allocation ratios. The inflation is quantified for two approaches: a naive procedure that ignores not only all modifications, but also the multiplicity issue arising from the many-to-one comparison, and a Dunnett procedure that ignores modifications, but adjusts for the initially started multiple treatments. The maximum inflation of the type 1 error rate for such types of design can be calculated by searching for the "worst case" scenarios, that are sample size adaptation rules in the interim analysis that lead to the largest conditional type 1 error rate in any point of the sample space. To show the most extreme inflation, we initially assume unconstrained second stage sample size modifications leading to a large inflation of the type 1 error rate. Furthermore, we investigate the inflation when putting constraints on the second stage sample sizes. It turns out that, for example fixing the sample size of the control group, leads to designs controlling the type 1 error rate.

Gewandter, Jennifer S., Robert H. Dworkin, Dennis C. Turk, Michael P. McDermott, Ralf Baron, Marc R. Gastonguay, Ian Gilron et al. "Research designs for proof-of-concept chronic pain clinical trials: IMMPACT recommendations." PAIN® (2014).

Proof-of-concept (POC) clinical trials play an important role in developing novel treatments and determining whether existing treatments may be efficacious in broader populations of patients. The goal of most POC trials is to determine whether a treatment is likely to be efficacious for a given indication and thus whether it is worth investing the financial resources and participant exposure necessary for a confirmatory trial of that intervention. A challenge in designing POC trials is obtaining sufficient information to make this important go/no-go decision in a cost-effective manner. An IMMPACT consensus meeting was convened to discuss design considerations for POC trials in analgesia, with a focus on maximizing power with limited resources and participants. We present general design aspects to consider including patient population, active comparators and placebos, study power, pharmacokinetic–pharmacodynamic relationships, and minimization of missing data. Efficiency of single-dose studies for treatments with rapid onset is discussed. The trade-off between parallel-group and crossover designs with respect to overall sample sizes, trial duration, and applicability is summarized. The advantages and disadvantages of more recent trial designs, including N-of-1 designs, enriched designs, adaptive designs, and sequential parallel comparison designs, are summarized, and recommendations for consideration are provided. More attention to identifying efficient yet powerful designs for POC clinical trials of chronic pain treatments may increase the percentage of truly efficacious pain treatments that are advanced to confirmatory trials while decreasing the percentage of ineffective treatments that continue to be evaluated rather than abandoned.

Koenig, Franz, Jim Slattery, Trish Groves, Thomas Lang, Yoav Benjamini, Simon Day, Peter Bauer, and Martin Posch. "Sharing clinical trial data on patient level: Opportunities and challenges." Biometrical Journal (2014).

In recent months one of the most controversially discussed topics among regulatory agencies, the pharmaceutical industry, journal editors, and academia has been the sharing of patient-level clinical trial data. Several projects have been started such as the European Medicines Agency´s (EMA) "proactive publication of clinical trial data", the *BMJ* open data campaign, or the AllTrials initiative. The executive director of the EMA, Dr. Guido Rasi, has recently announced that clinical trial data on patient level will be published from 2014 onwards (although it has since been delayed). The EMA draft policy on proactive access to clinical trial data was published at the end of June 2013 and open for public consultation until the end of September 2013. These initiatives will change the landscape of drug development and publication of medical research. They provide unprecedented opportunities for research and research synthesis, but pose new challenges for regulatory authorities, sponsors, scientific journals, and the public. Besides these general aspects, data sharing also entails intricate biostatistical questions such as problems of multiplicity. An important issue in this respect is the interpretation of multiple statistical analyses, both prospective and retrospective. Expertise in biostatistics is needed to assess the interpretation of such multiple analyses, for example, in the context of regulatory decision-making by optimizing procedural guidance and sophisticated analysis methods.

Alonso, Ariel, Wim Van der Elst, Geert Molenberghs, Marc Buyse, and Tomasz Burzykowski. "On the relationship between the causal-inference and meta-analytic paradigms for the validation of surrogate endpoints." Biometrics (2014).

The increasing cost of drug development has raised the demand for surrogate endpoints when evaluating new drugs in clinical trials. However, over the years, it has become clear that surrogate endpoints need to be statistically evaluated and deemed valid, before they can be used as substitutes of “true” endpoints in clinical studies. Nowadays, two paradigms, based on causal-inference and meta-analysis, dominate the scene. Nonetheless, although the literature emanating from these paradigms is wide, till now the relationship between them has largely been left unexplored. In the present work, we discuss the conceptual framework underlying both approaches and study the relationship between them using theoretical elements and the analysis of a real case study. Furthermore, we show that the meta-analytic approach can be embedded within a causal-inference framework on the one hand and that it can be heuristically justified why surrogate endpoints successfully evaluated using this approach will often be appealing from a causal-inference perspective as well, on the other. A newly developed and user friendly R package *Surrogate* is provided to carry out the evaluation exercise.

Senn, Stephen. "A note regarding meta-analysis of sequential trials with stopping for efficacy." Pharmaceutical statistics 13, no. 6 (2014): 371-375.

It is shown that fixed-effect meta-analyses of naïve treatment estimates from sequentially run trials with the possibility of stopping for efficacy based on a single interim look are unbiassed (or at the very least consistent, depending on the point of view) provided that the trials are weighted by information provided. A simple proof of this is given. An argument is given suggesting that this also applies in the case of multiple looks. The implications for this are discussed.

Tamm, M., and R-D. Hilgers. "Chronological Bias in Randomized Clinical Trials Arising from Different Types of Unobserved Time Trends." Methods Inf Med 53 (2014): 501-510.

Background: In clinical trials patients are commonly recruited sequentially over time incurring the risk of chronological bias due to (unobserved) time trends. To minimize the risk of chronological bias, a suitable randomization procedure should be chosen.

Objectives: Considering different time trend scenarios, we aim at a detailed evaluation of the extent of chronological bias under permuted block randomization in order to provide recommendations regarding the choice of randomization at the design stage of a clinical trial and to assess the maximum extent of bias for a realized sequence in the analysis stage.

Methods: For the assessment of chronological bias we consider linear, logarithmic and stepwise trends illustrating typical changes during recruitment in clinical practice. Bias and variance of the treatment effect estimator as well as the empirical type I error rate when applying the t-test are investigated. Different sample sizes, block sizes and strengths of time trends are considered.

Results: Using large block sizes, a notable bias exists in the estimate of the treatment effect for specific sequences. This results in a heavily inflated type I error for realized worst-case sequences and an enlarged mean squared error of the treatment effect estimator. Decreasing the block size restricts these effects of time trends. Already applying permuted block randomization with two blocks instead of the random allocation rule achieves a good reduction of the mean squared error and of the inflated type I error. Averaged over all sequences, the type I error of the t-test is far below the nominal significance level due to an overestimated variance.

Conclusions: Unobserved time trends can induce a strong bias in the treatment effect estimate and in the test decision. Therefore, already in the design stage of a clinical trial a suitable randomization procedure should be chosen. According to our results, small block sizes should be preferred, but also medium block sizes are sufficient to restrict chronological bias to an acceptable extent if other contrary aspects have to be considered (e.g. serious risk of selection bias). Regardless of the block size, a blocked ANOVA should be used because the t-test is far too conservative, even for weak time trends.

Graf, Alexandra C., Martin Posch, and Franz Koenig. "Adaptive designs for subpopulation analysis optimizing utility functions." Biometrical Journal (2014).

If the response to treatment depends on genetic biomarkers, it is important to identify predictive biomarkers that define (sub-)populations where the treatment has a positive benefit risk balance. One approach to determine relevant subpopulations are subgroup analyses where the treatment effect is estimated in biomarker positive and biomarker negative groups. Subgroup analyses are challenging because several types of risks are associated with inference on subgroups. On the one hand, by disregarding a relevant subpopulation a treatment option may be missed due to a dilution of the treatment effect in the full population. Furthermore, even if the diluted treatment effect can be demonstrated in an overall population, it is not ethical to treat patients that do not benefit from the treatment when they can be identified in advance. On the other hand, selecting a spurious subpopulation increases the risk to restrict an efficacious treatment to a too narrow fraction of a potential benefiting population. We propose to quantify these risks with utility functions and investigate nonadaptive study designs that allow for inference on subgroups using multiple testing procedures as well as adaptive designs, where subgroups may be selected in an interim analysis. The characteristics of such adaptive and nonadaptive designs are compared for a range of scenarios.

Klinglmueller, Florian, Martin Posch, and Franz Koenig. "Adaptive graph-based multiple testing procedures." Pharmaceutical statistics 13, no. 6 (2014): 345-356.

Multiple testing procedures defined by directed, weighted graphs have recently been proposed as an intuitive visual tool for constructing multiple testing strategies that reflect the often complex contextual relations between hypotheses in clinical trials. Many well-known sequentially rejective tests, such as (parallel) gatekeeping tests or hierarchical testing procedures are special cases of the graph based tests. We generalize these graph-based multiple testing procedures to adaptive trial designs with an interim analysis. These designs permit mid-trial design modifications based on unblinded interim data as well as external information, while providing strong family wise error rate control. To maintain the familywise error rate, it is not required to prespecify the adaption rule in detail. Because the adaptive test does not require knowledge of the multivariate distribution of test statistics, it is applicable in a wide range of scenarios including trials with multiple treatment comparisons, endpoints or subgroups, or combinations thereof. Examples of adaptations are dropping of treatment arms, selection of subpopulations, and sample size reassessment. If, in the interim analysis, it is decided to continue the trial as planned, the adaptive test reduces to the originally planned multiple testing procedure. Only if adaptations are actually implemented, an adjusted test needs to be applied. The procedure is illustrated with a case study and its operating characteristics are investigated by simulations.

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