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# **IDeAI**

*Integrated Design and Analysis of small  
population group trials*

## **A Collaborative Approach between Industry and Academia**

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Isaac Newton Institute, Cambridge





## ***Background of FP7 - Call***

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*New methodologies for clinical trials for small population groups*

FP7-HEALTH-2013-INNOVATION-1.

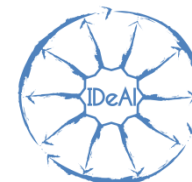
### Objective

develop **new or improved statistical design methodologies** for clinical trials aiming at the efficient assessment of the safety and/or efficacy of a treatment for small population **groups in particular for rare diseases or personalised (stratified or individualised) medicine.**

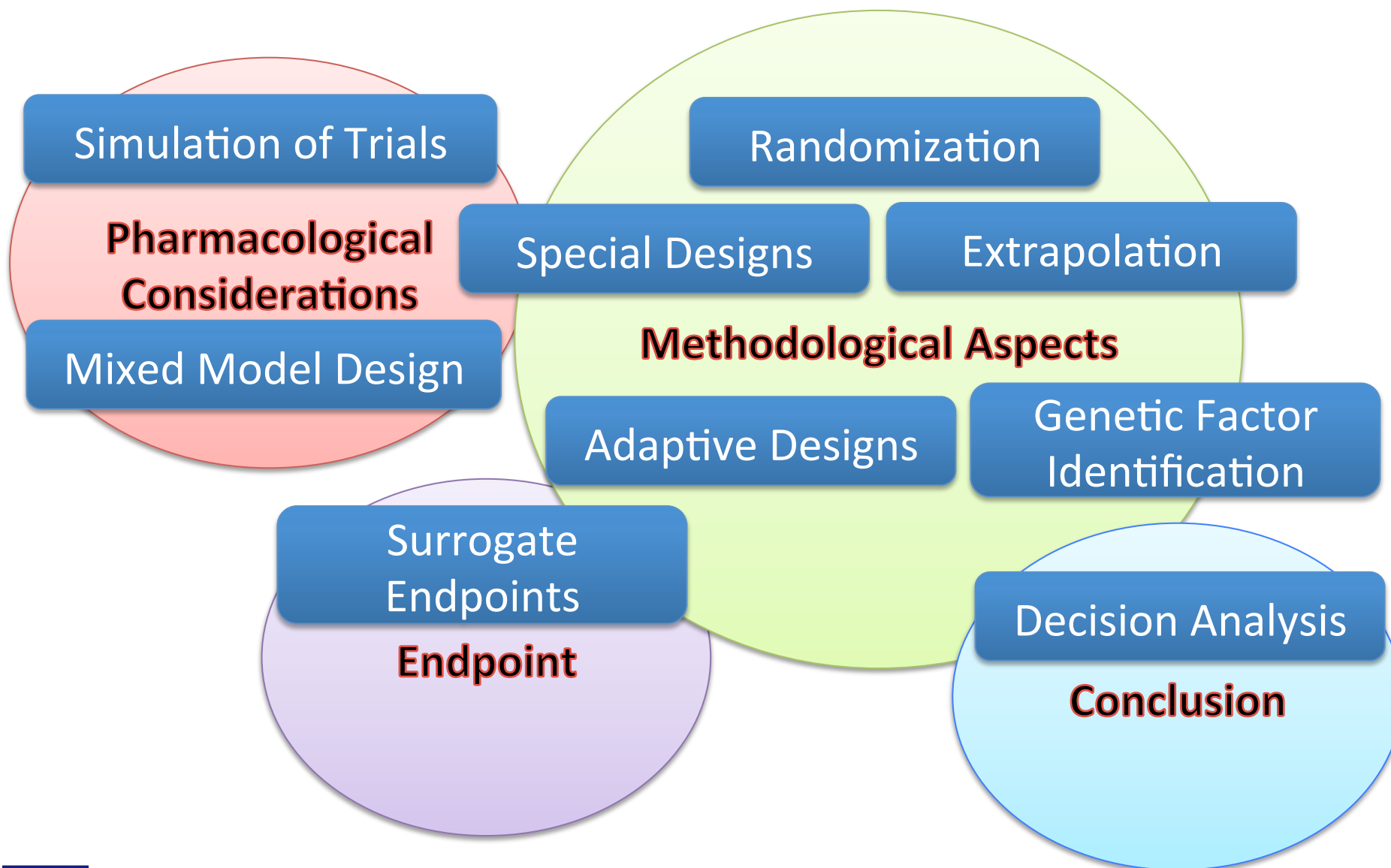
### Expected Impact

- **Cost efficient clinical trials deriving reliable results** from trials in small population groups.





# Identified Methods / Targets



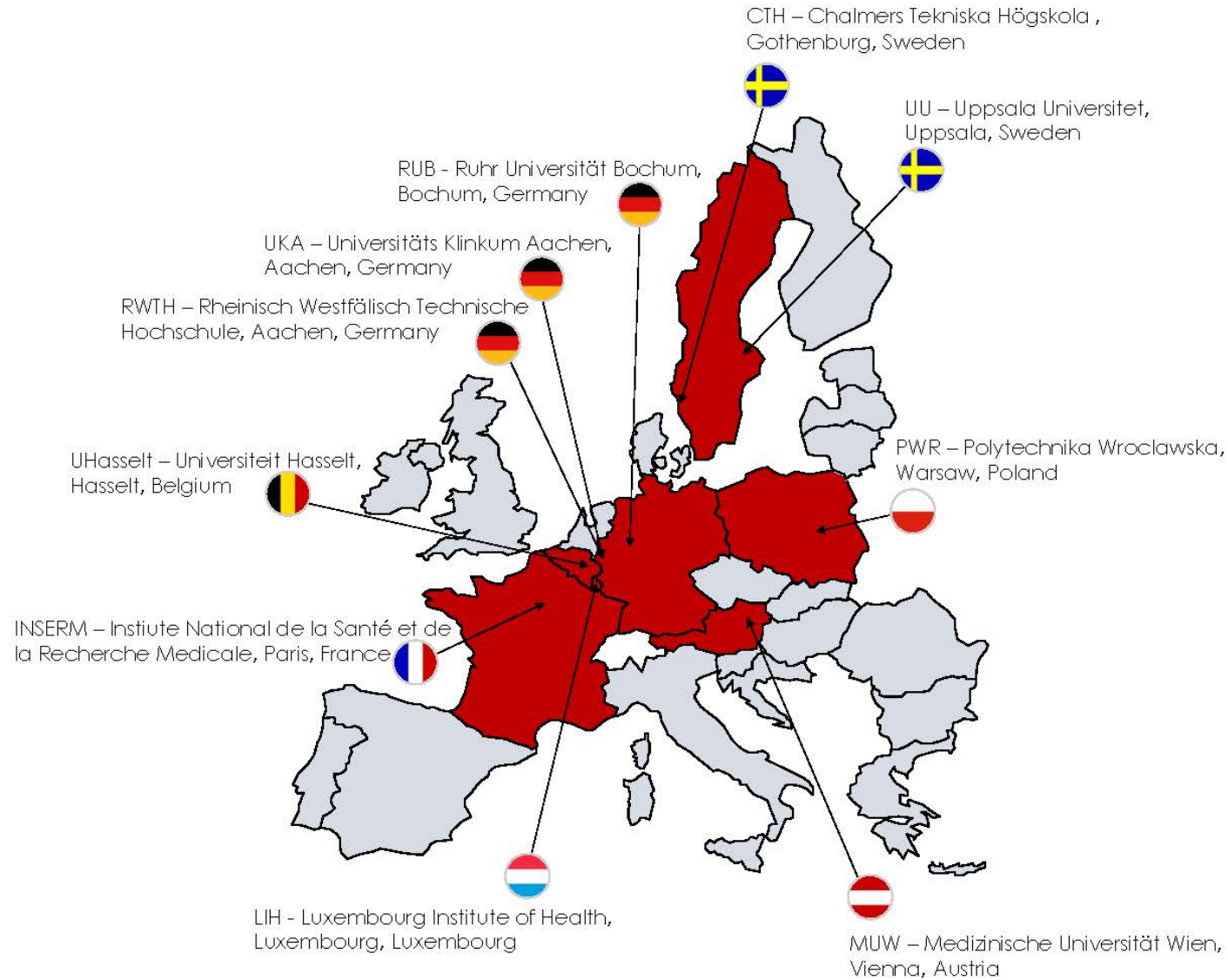


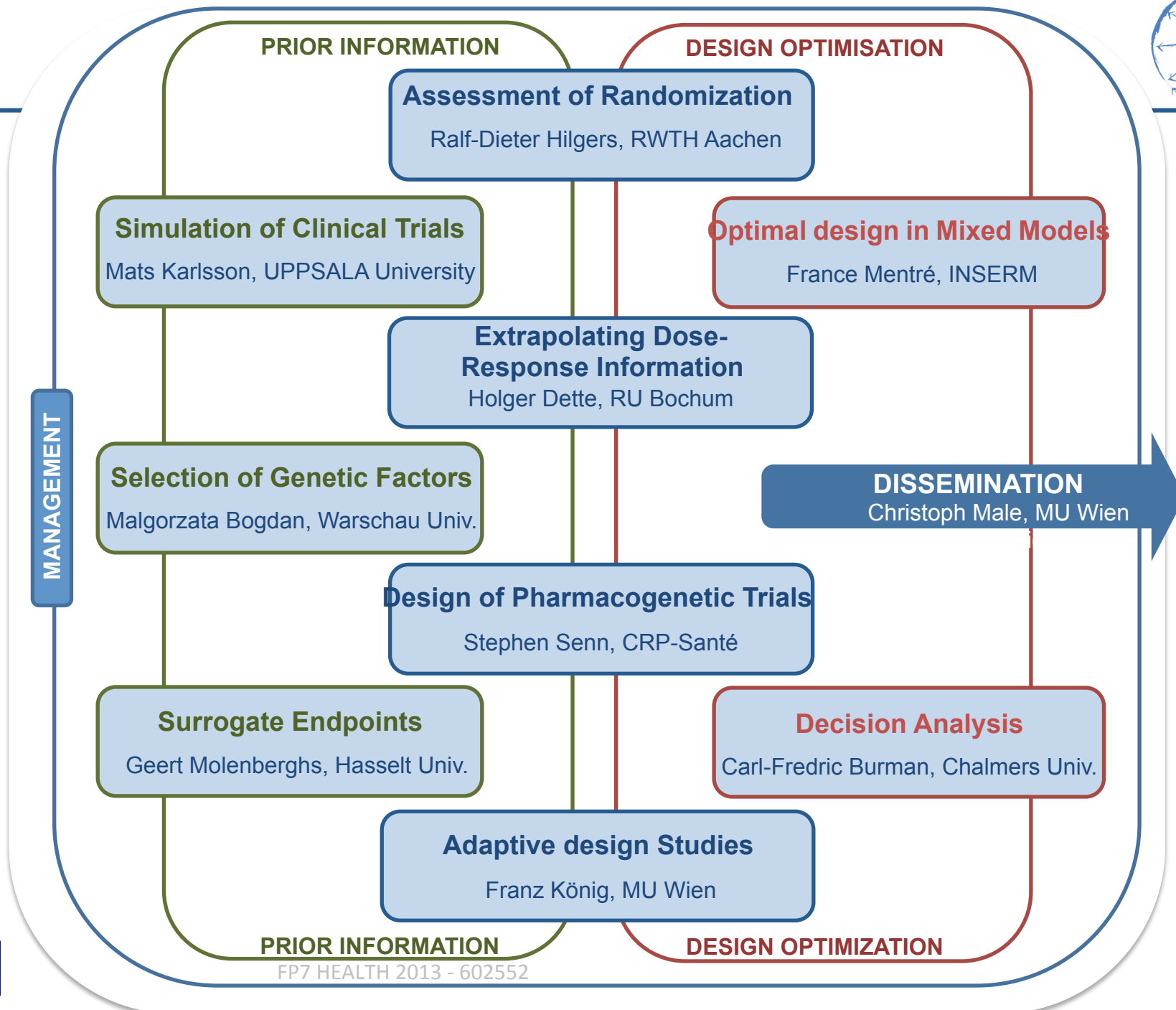
### **Integrated DDesign and AnaLysis** of small population group trials

- to refine the statistical methodology for clinical trials in small population groups by strictly following the concept of an improved integration of design, conduct and analysis of clinical trials from various perspectives.



# IDeAI Consortium







## Workpackage 2 – *Prof. Dr. Ralf-Dieter Hilgers*

- **Development of the most appropriate randomisation procedure for small population group clinical trials and the recommendation of the corresponding randomisation based test procedure**
- *Bias assessment of randomisation procedures*
- *Development of adequate randomisation procedures for small population groups*
- *Development of randomisation test for small population groups*





## Workpackage 3 - *Prof. Dr. Holger Dette*

- **Developing a rigorous statistical methodology for extrapolation of dose response information available from a given source population to make inference for another target population which is much smaller in size**
- New statistical measures for similarity of dose-response between a source and a target population
- Robustness against incorrect model assumptions
- Minimisation of false claims through optimal experimental design





## Workpackage 4 - *Prof. Dr. Franz König*

- **Develop methods to incorporation of external information into adaptively designed clinical studies for small population groups**
- Developing adaptive methods to define the level of evidence required in small population groups trials
- Developing adaptive clinical trial designs to confirmatory demonstrating of efficacy
- Developing adaptive designs for comparative effectiveness analysis





## Workpackage 5 – *Prof. Dr. France Mentré*

- **Develop optimal designs in non-linear mixed effects (NLME) models to analyse studies in small population groups.**
- Extend and evaluate the existing approach to calculate the FIM for longitudinal models with discrete data, repeated time to event and joint models
- Propose robust approaches with respect to parameter values as two-stage adaptive designs
- Propose robust approaches with respect to model uncertainty in design and analysis of pivotal trials analysed through modelling





## Workpackage 6 - *Prof. Dr. Stephen Senn*

- **Designing pharmacogenetic small population group trials including cross-over trials, n-of-1 trials and enrichment trials**
- Identification of conditions that have to be met for personalising therapy
- Development of practical and useable n-of-1 (or repeated cross-over) templates for those disease areas where repeated treatment of patients is possible
- Development of suitable approaches to analysing subgroups for those diseases where cross-over trials are not possible
- Establishing approaches to sample-size determination that take account of the value of information





## Workpackage 7 - *Prof. Dr. Mats Karlsson*

- **Simulation of clinical trials in small population groups based on non-linear mixed effects (NLME) models**
- Develop and evaluate the performance of a parametric power estimation (PPE) algorithm for faster sample size calculations
- Investigate type I error rate and power to detect drug effects in parallel and cross-over trials with within-subject parameter variability (WSV)
- Propose methods for calibration using permutation tests





## Workpackage 8 - *Prof. Dr. Malgorzata Bogdan*

- **Development of new statistical models for prediction of the response to the therapy in small population group trials based on genetic factors and other covariates**
- Bayesian methods for identification of genetic pathways involved in the development of disease and the response to the therapy
- Development and application of high dimensional model selection for identification of regulatory regions influencing detected pathways
- Statistical model relating response to the therapy in small population group trials based on identified genetic factors and other covariates, as well as their interactions





## Workpackage 9 – *Prof. Dr. Carl-Fredrik Burman*

- **Improvement of the rational basis for decisions, and help align different stakeholder perspectives.**
- Demonstrate that uncertainty in regulatory/payer decision rules may translate into suboptimal designs
- Apply Bayesian decision theoretic framework in case where the priors for efficacy and safety may be more or less conservative for different stakeholders
- Optimise the design of clinical trials for small population groups for fixed post-trial stakeholder decision rules





## Workpackage 10 - *Prof. Dr. Geert Molenberghs*

- **Develop an efficient and feasible framework for biomarker and surrogate endpoints in small population group clinical trials**
- Establish a viable framework for biomarker and surrogate endpoint evaluation in small population groups with proper incorporation of missing-data aspects
- Using to a maximal extent design aspects: randomisation methodology, optimal design, adaptive designs, decision theory, mixed models, cross-over trials, genetic markers, dose-response information
- Develop simulation-based and other efficient estimation and evaluation methods





# Design in small RCT: Algorithm of choice

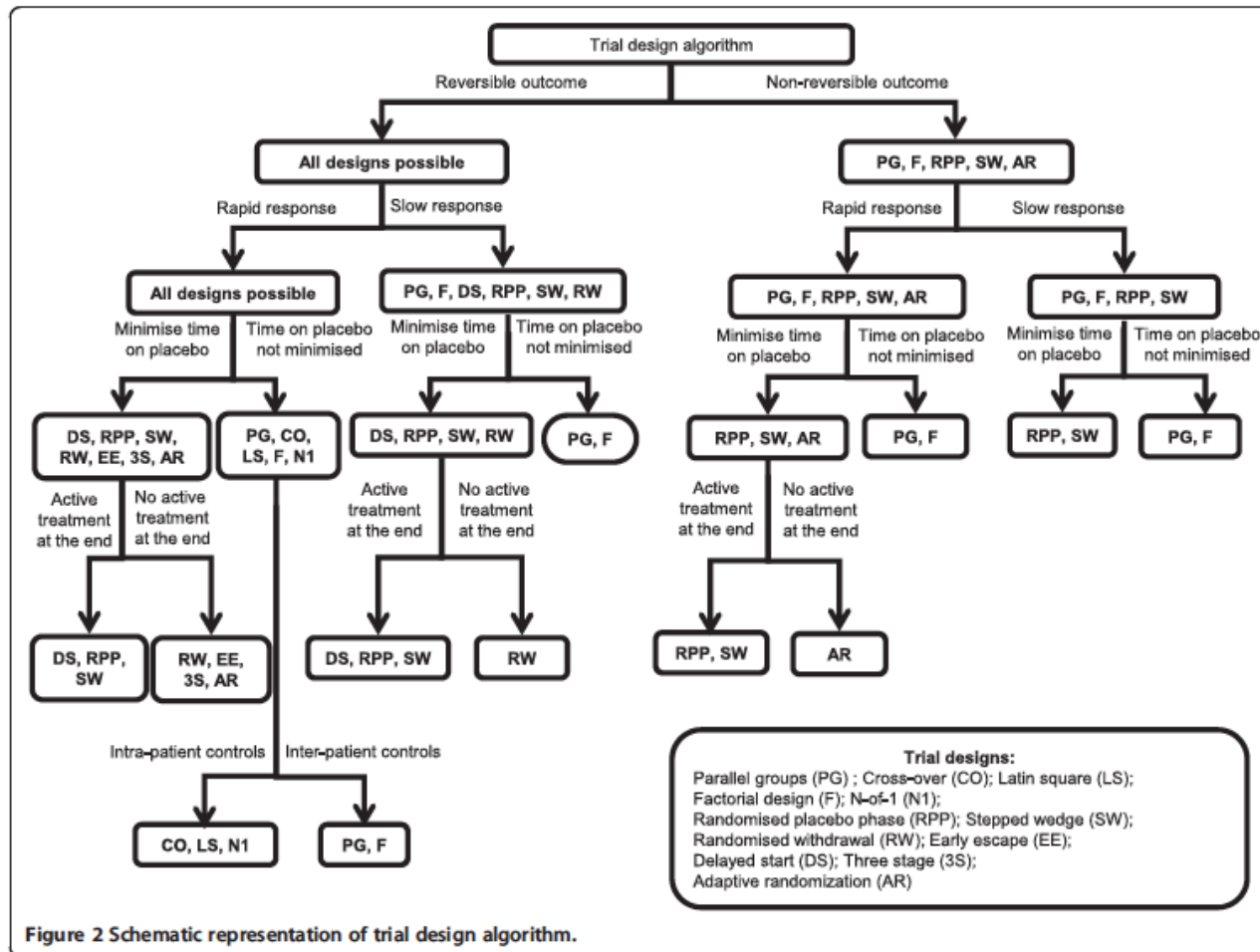


Figure 2 Schematic representation of trial design algorithm.

CRESim project (Rare disease: use of clinical trial simulation for the choice and optimisation of study design)  
 Cornu et al. Orphanet Journal of Rare Diseases 2013

## Traditional Designs:

- **Parallel Group**
- **Crossover**
- Factorial
- Add-on
- Randomized Withdrawal
- Early Escape

## Special Designs:

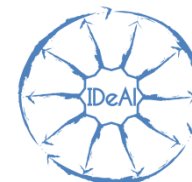
- **N-of-1**
- Sequential
- **Decision analysis based**
- **Ranking & selection**
- **Adaptive**
- **Risk based allocation**

## Analysis Approaches

- **Sequential Analysis**
- **Hierarchical Analysis**
- **Bayesian Analysis**
- **Decision Analysis**
- Statistical Prediction
- **Meta Analysis**
- **Risk-based allocation**







# External Advisory Board

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8	Chris Jennison	Bath (GB)

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# IRDiRC Task Force on Small Population Clinical Trials



Collaborative effort on adaptive design, statistical methods and acceptability of new methods in small population clinical trials resulting in agreement between all stakeholders on appropriate designs for small population studies



Members are

- Ralf-Dieter Hilgers, IDEAL
- Ilan Irony, FDA
- Jordi Llinares, EMA
- Kit Roes, ASTERIX
- Nigel Stallard, INSPIRE





## Conclusion after 18 month

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- Published 12 Papers
- Comments on regulatory documents
- 9 papers are currently under review
- Special Sessions to 7 Conferences
- Presentations and workshops at several Conferences and Workshops (AISC, ISCB, MCP, Sim. Workshop, WS in London etc.)



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