IDEAL
Integrated Design and Analysis of small population group trials

DIA ADSWG Meeting 2014-02-28

Ralf-Dieter Hilgers
Carl-Fredrik Burman
Franz Koenig

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

FP7 HEALTH 2013 - 602552

Outlook

- SPG; why current drug development approaches are not addressing them appropriately
- Overview of the grant, consortium structure, 11 WPs
- Focus on two work packages:
  - Decision Analysis
  - Adaptive design
- Plans for collaboration with DIA ADSWG

The Problem

Rare disease

- European Community: 5 to 10000
- E.g. Gaumenspalte 50/100 000, CDG-Syndrom Typ Ij 1 case, Fine-Lubinsky-Syndrom 5 cases, Tietz-Syndrom 1 family

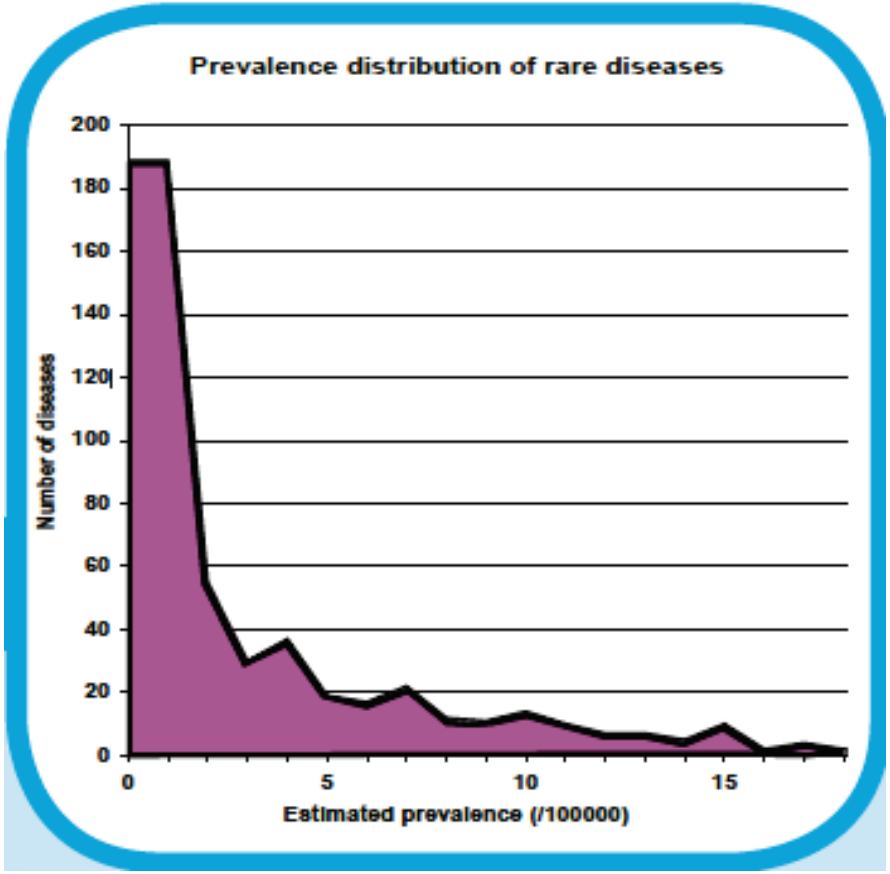
Subgroup Analysis

- Therapy Responder

Treatments

- Drugs
- Surgical procedures
- Medical Devices etc.

Orphanet, 2012



Embedding

- EURORDIS – The Voice of Rare Disease Patients in Europe

- National plans or strategies for rare diseases
- EU initiatives on rare diseases

- Orphanet (The portal for rare diseases)

- International Rare Diseases Research Consortium (IRDiRC) 2011

Orphan Drug Use in Rare Disease

- Transfer from animals to human
- Design
- Building computational models of a disease and simulate trial designs
- Outcomes – scores
- Long term survival
- Identify biomarker
- Mirror clinical pathways
- Extrapolation

Remember the Call

New methodologies for clinical trials for small population groups

FP7-HEALTH-2013-INNOVATION-1.

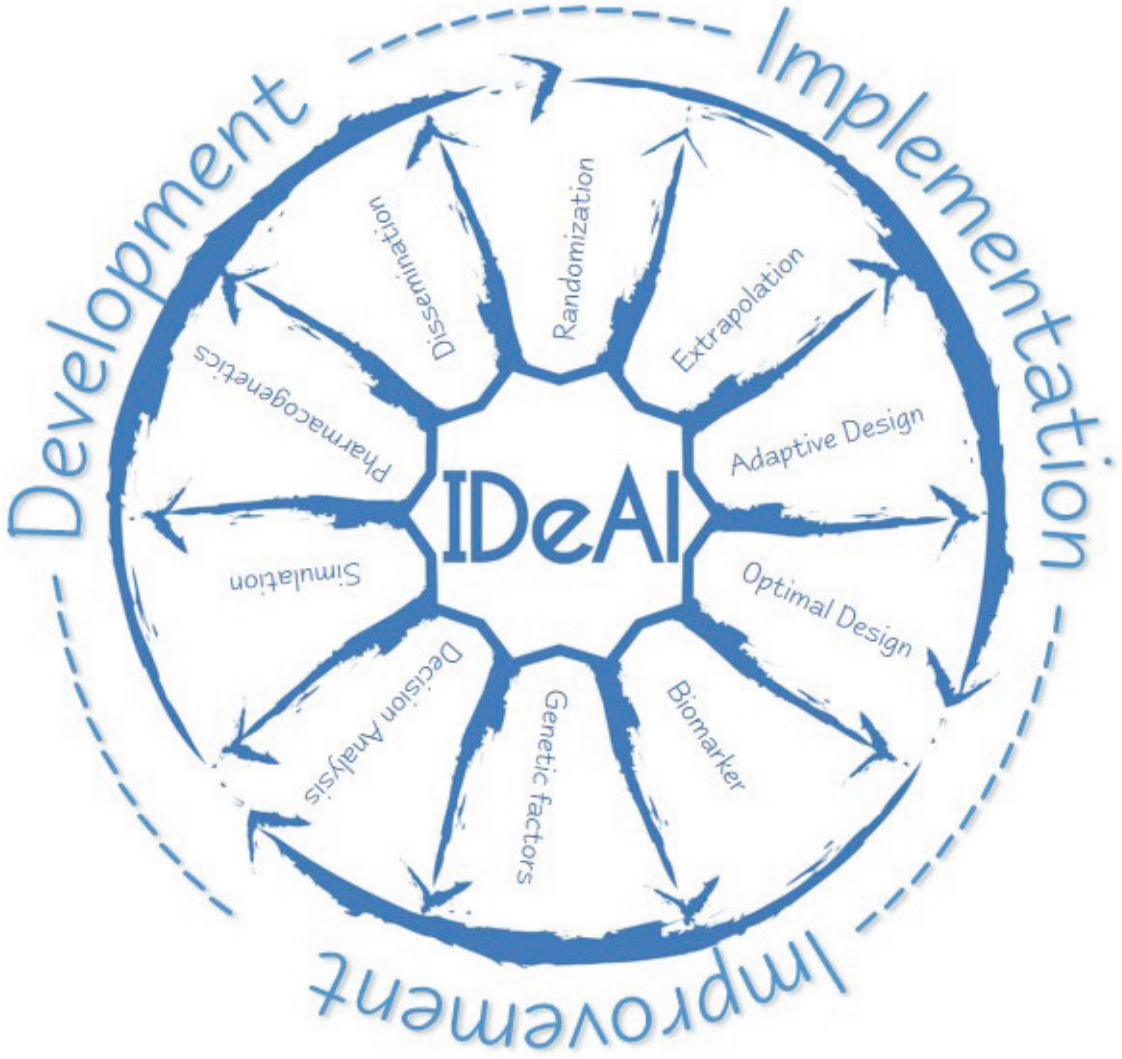
Objective

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.

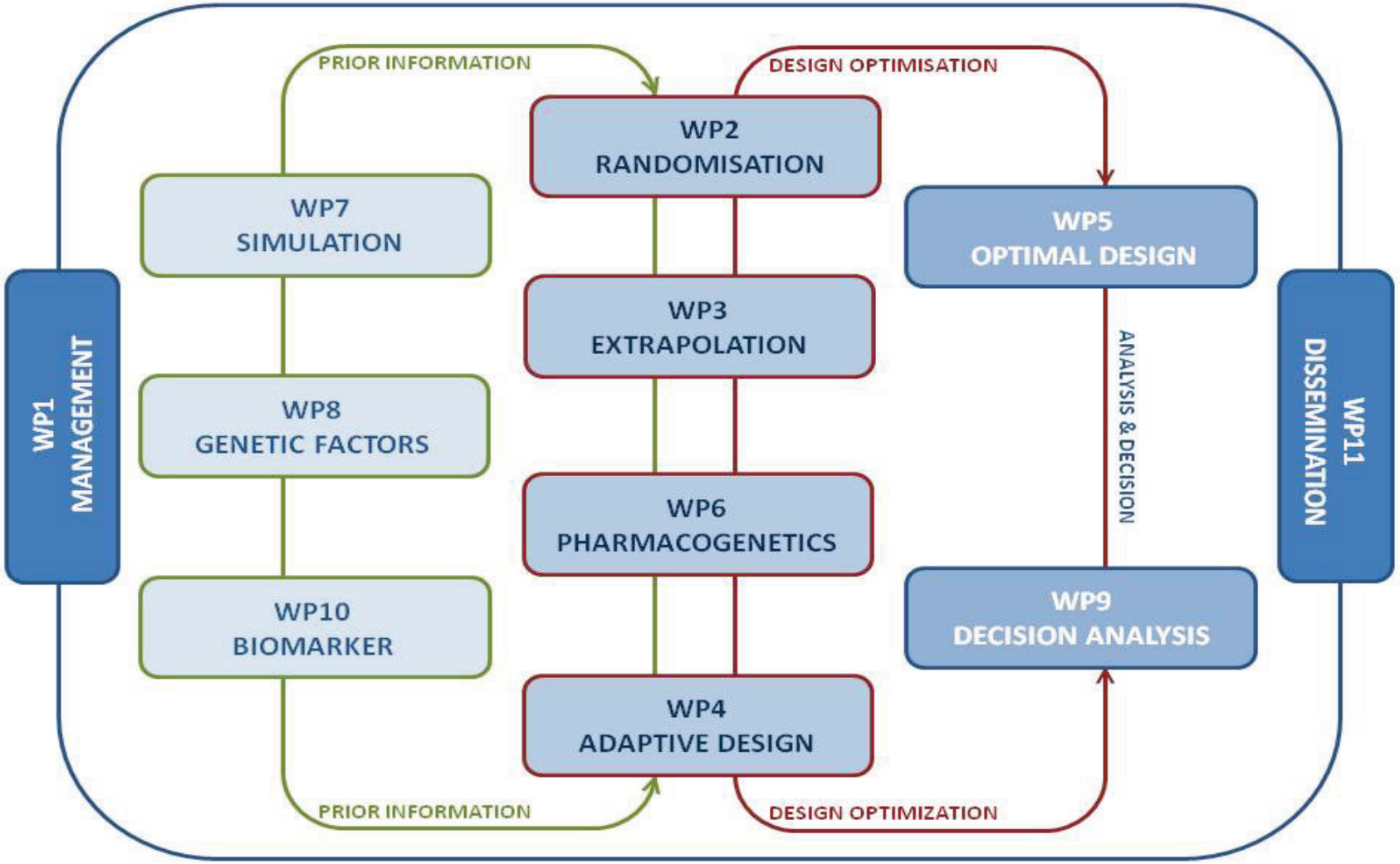
IDEAL Project (started on 1st Nov 2013)



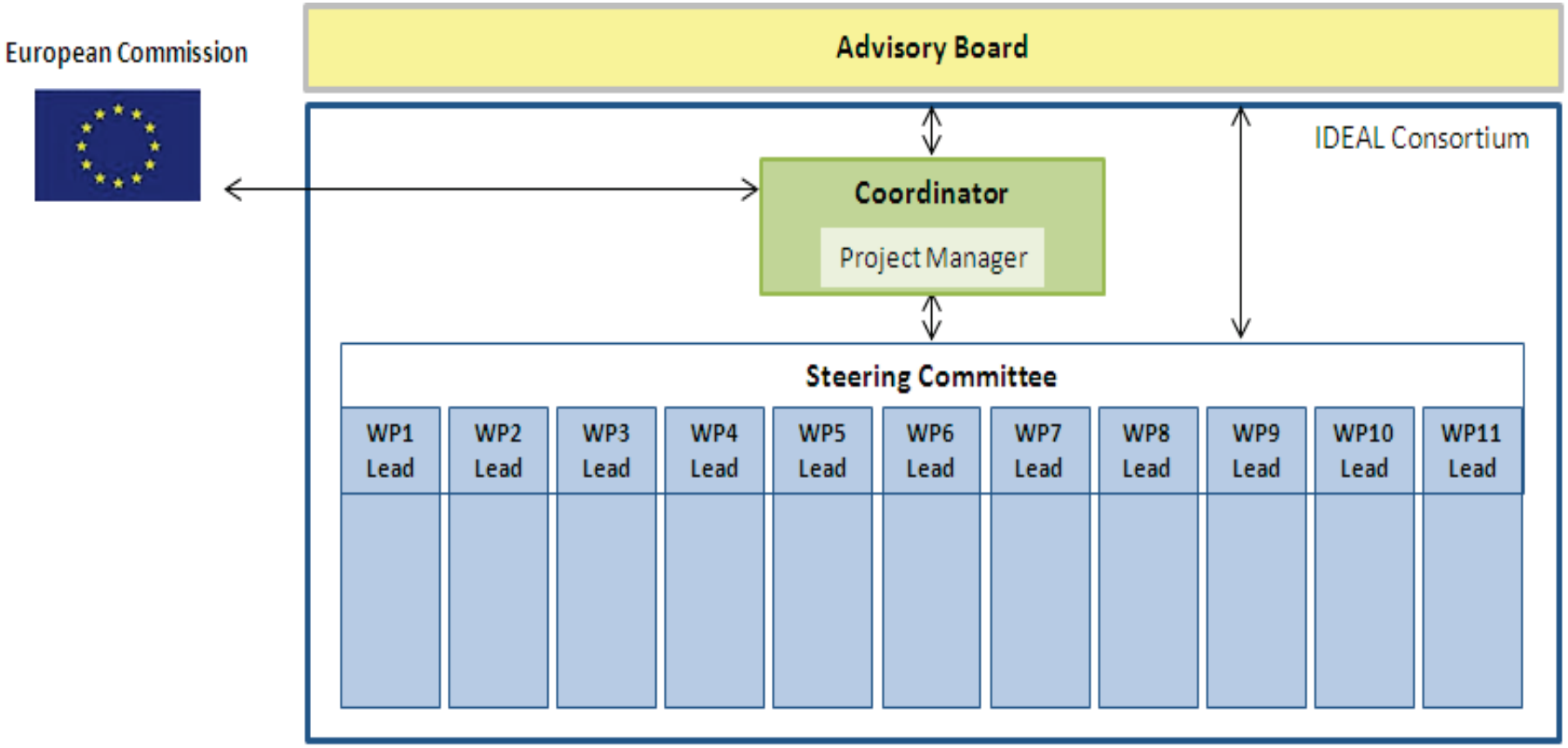
IDEAL Work Packages and PIs

Assessment of randomisation procedures and randomisation based test in small population groups	**Ralf-Dieter Hilgers (project lead of IDEAL)** RWTH Aachen, Germany
Extrapolating dose response information to small population groups	**Holger Dette** Ruhr Universität Bochum, Germany
Adaptive design studies in small population groups	**Franz König** Medical University of Vienna, Austria
Optimal design in mixed models to analyse studies in small population groups	**France Mentré** INSERM, France
Design of pharmacogenetic small population groups trials including, crossover trials, n-of-1 trials and enrichment trials	**Stephen Senn** CRP SANTÉ, Luxembourg
Simulation of clinical trials in small population groups	**Mats Karlsson** Uppsala University, Sweden
Genetic factors influencing the response to the therapy in small population group trials	**Malgorzata Bogdan** POLITECHNIKA WROCŁAWSKA,Poland
Decision analysis in small population groups	**Carl-Fredrik Burman** Chalmers Univeristy, Sweden
Biomarker surrogate endpoints in small population groups	**Geert Molenberghs** Universiteit Hasselt & KU Leuven, Belgium
Dissemination of results	**Christoph Male (pediatrician, PDCO member)** Medical University of Vienna, Austria

Workpackages



Management Structure



External Scientific Advisory Board

Regulators, patient representatives, clinicians, statisticians, …

Name	Institution
Dr. Jordi Llinares, Dr Ralf Herold	European Medicines Agency
Dr. Gerard Nguyen	Rett Syndrome Europe, PDCO patient representative member (EURORDIS),Member of EUCERD,…
Dr. Odile Kremp	Director of Orphanet
Prof. Gerard Pons	PU-PH/CS chez Univ Paris Descartes APHPPU-PH/CS chez Univ Paris Descartes APHPUniv Paris Descartes APHP
Prof. Tomasz Burzykowski	IDDI Inc., (International Drug Development Institute)
Dr. Paolo Baroldi	Vanda Pharmaceuticals Inc
Prof. Gernot Wassmer	AptivSolutions
Prof. Frank Bretz	Novartis Pharma
Prof. Rosemary Bailey	School of Mathematics and Statistics, University of St Andrews
Dr. Martin Forster	Department of Economics and Related Studies, University of York
Prof. Steven A. Julious	Medical Statistics Group, The University of Sheffield
Dr Paolo Pertile	Faculty of Economics, Verona University
Prof. William F. Rosenberger	Department of Statistics, George Mason University
Prof. Chiara Sabatti	Associate Professor of Health Research and Policy and of Statistics at Stanford
Prof. Günther Schmalzing	Department of Molecular Pharmacology, RWTH Aachen, Germany / Lead of Ethics Committee RWTH Aachen
Prof. Christopher Jennison	Department of Mathematical Sciences , University of Bath

RANDOMISATION
Workpackage 2 – *Ralf-Dieter Hilgers*

Name: Assessment of randomisation procedures and randomisation based test in small population groups

Deliverables

2.1. Bias assessment of randomisation procedures

2.2. Development of adequate randomisation procedures for small population groups

2.3. Development of randomisation test for small population groups

Work Package 9
DECISION ANALYSIS IN SMALL POPULATION GROUPS

Work package leader:
Carl-Fredrik Burman
Chalmers University

Background

- The Decision Analysis (DA) work package is partly inspired by the work in the DIA ADSWG Adaptive Programme (AP) wks
  - Decision theoretic
  - Bayesian "in-house" + perhaps frequentist to costumer (foretelling stakeholder analysis)
  - Study optimisation
  - Programme optimisation

Objectives (following grant application)

- "… to improve the rational basis for decisions,
- and help align different stakeholder perspectives.

(Method)

- A Bayesian decision theoretic framework will be applied, but the priors for efficacy and safety may be more or less conservative for different stakeholders.
- In addition, pure frequentist decision rules will be considered for e.g. regulatory agencies."

Deliverables

- D9.1) Guidance regarding stakeholder decision rules: The deliverable will be a decision theoretic framework for the main decisions made by key stakeholders (patient, prescribing physician, HTAs, RAs) _ _ _ will include an analysis of the impact of certain stakeholder decisions on the expected clinical utility in the population.
- D9.2) … R code for the optimisation of confirmatory trials with respect to dose selection and sample size, given certain stakeholder decision rules (see D9.1).
- D9.3) … recommendations … for how decisions on late stage trial design and treatment utilisation in small populations should be taken by relevant stakeholders, using the decision theoretic framework. This include the late stage investment decisions taken by pharmaceutical companies, as well as regulatory approvals and reimbursement decisions. (Hoping for: programme optimisation)

Example: RA + sponsor; focus on efficacy

- Limited (small) population size, N
- Test NEW drug vs CONTROL in n patients
- Possible regulatory rules
  - No regulatory hurdle
  - One trial $p<0.025$ (or e.g. $p<0.1$)
  - Two trials $p<0.025$
- What is optimal trial (/program) size, n? Based on prior.
  - Optimal meaning "best outcome among N pat's" (societal perspective)
  - Optimal Net Present Value (commercial perspective)
  - Optimal for individual trial patient (ethical)
  - Adaptivity?

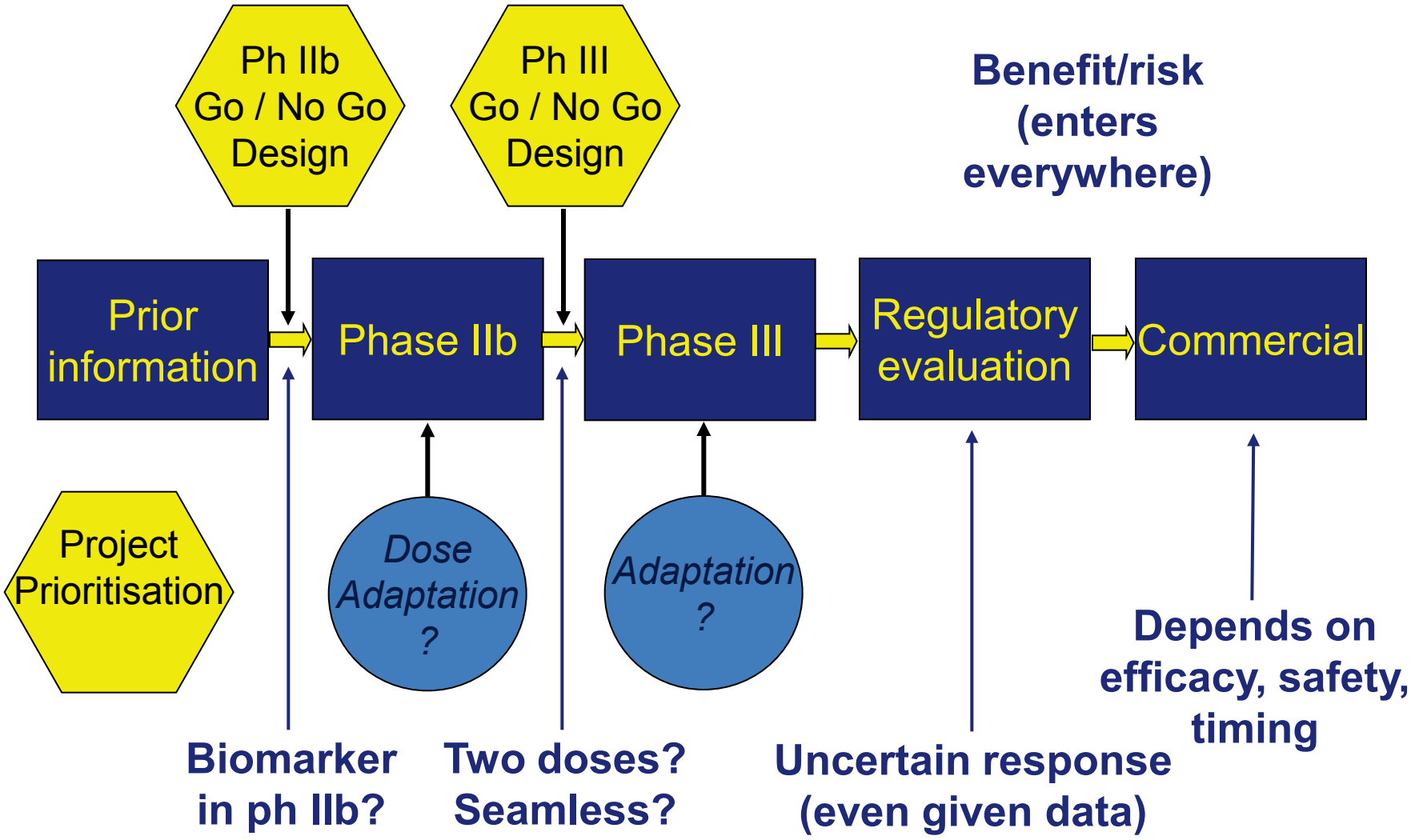
Variation: Include safety

- Estimated efficacy, E
- Estimated safety S
- Possible regulatory benefit/risk hurdles:
  - $S < K$ Estimated safety
  - $S + 1.96\ SE(S) < K'$ Non-inferiority
  - $E - c \cdot S > 0$ Estimated B/R
  - $E - c \cdot S - 1.96\ SE(E - c \cdot S) > 0$ Proven positive B/R
  - How would you model the RA decision rule?
- Optimise trial design, given priors.

Variations: some extensions

- As before, but add
  - Payer hurdle: e.g. based on estimated cost-effectiveness
  - Patient heterogeneity, modelling efficacy and safety as functions of patient covariates
  - Dose choice for phase III
  - Potential of two doses in phase III
  - Simultaneuos optimisation of programme design, including dose-response phase IIB and confirmatory phase III
  - Biomarker issue in study (/programme) design

AP potential model components



AP small population WG

- New working group, within DIA ADSWG Adaptive Programmes
- Co-chaired by Bob Beckman, Cong Chen
- 2nd TC a week ago
- Preliminary initial focus on treatment-predictive biomarker
  - Say that biomarker X is likely predicting treatment benefit (vs control)
  - For which values of X will NEW be beneficial?
  - How to design trial(s) to evaluate biomarker dependence and verify efficacy in a subpopulation?

IDEAL ♥ ADSWG

- All members of the Adaptive Programme core team (at that time) were mentioned in the grant application as supporting IDEAL
- New AP small population WG
- Membership overlap
- Volunteers for collaborations?

Organisation of WP9 Decision Analysis

- Led from Chalmers Univ, Sweden
- Collaboration with other universities
- Principal investigator: Carl-Fredrik Burman
- PhD student: Sebastian Jobjörnsson
- Senior researcher: Petter Mostad
- Ongoing collaborations
  - Martin Forster, Paolo Pertile (Health Economics)
  - DIA small population WG

Work Package 4
ADAPTIVE DESIGNS

Work package leader:
Franz Koenig
Medical University of Vienna, Austria

Medical University of Vienna – what? who?

- Medical University of Vienna (MUW)
- Center for Medical Statistics, Informatics, and Intelligent Systems (CEMSIIS)
- Section of Medical Statistics (IMS)

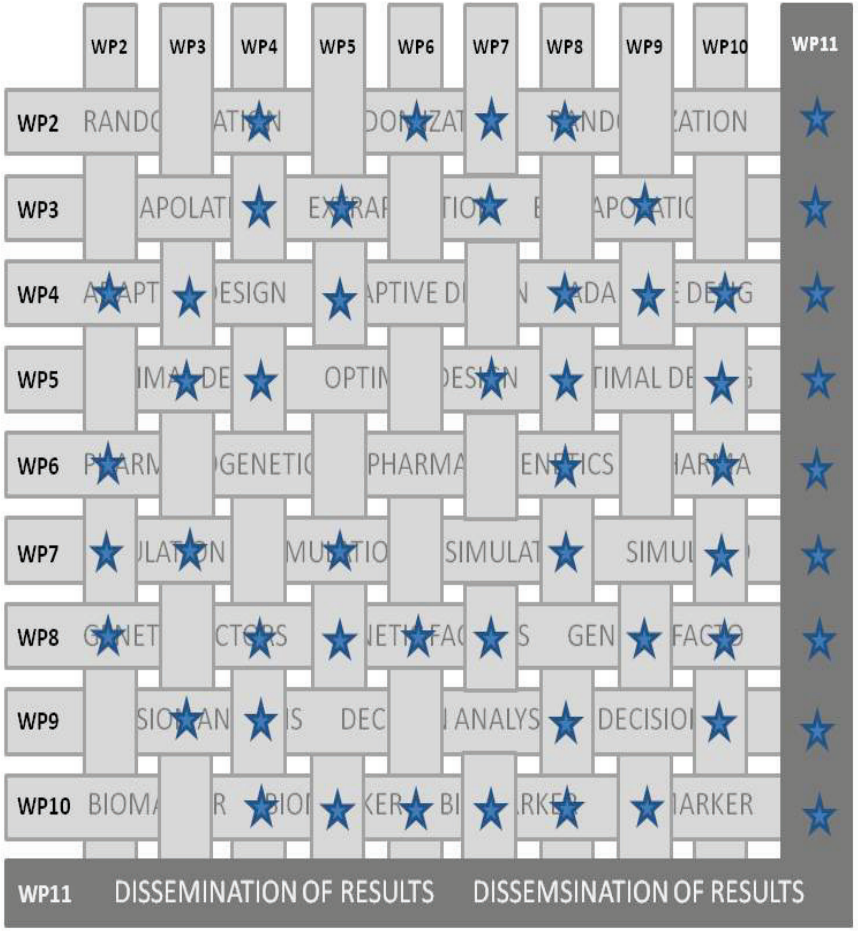
- Head (since 2012): Prof. Martin Posch

- Emeritus Prof. Peter Bauer

- Head of working group „Adaptive Designs“: Franz König

- See www.meduniwien.ac.at/medstat

Who is supposed to do the work in WP4?



MUW Permanent staff:
Peter Bauer
Franz König (PI IDEAL WP Adaptive)
Florian Klinglmüller

MUW – 2 IDEAL PhD students:
Gerald Hlavin
Sergey Krasnozhon

Two stays abroad planned:
Novartis, Basel (1month)
AptivSolution, Cologne (1 month)

UKA, RUB, PWR, CTH, …

… AND HOPEFULLY WE WILL COLLABORATE WITH DIA ADSWG AND ITS WGs

Classical Clinical Trials with pre-specified Design

Pre-specified Design Parameters:

- Sample Size
- Population
- Treatments (doses)
- Outcome variable(s)

- Dealing with the unexpected?
- Classical fixed trial paradigm allow little learning during the conduct of the trial.

Medical Statistician: one who will not accept that Columbus discovered America … because he said he was looking for India in the trial plan. (* A cross over trial)*
Stephen Senn, 1997, p 58

"Fully" adaptive (flexible) designs

Adaptive or flexible designs allow for mid-trial design modifications based on information from in- and outside the trial without compromising on the false positive error rate (and hopefully improving the performance of the running trial).

To control the type I error, the design modifications need not be specified in advance!

Bauer (1989), Bauer and Koehne (1994), Proschan and Hunsberger (1995), Bauer & Kieser (1999), Müller & Schäfer (2001, 04), Posch and Proschan (2012), Posch et al. 2005, Bretz et al. (2006), König et al. 2007, Brannath et al. 2009, ...

Three main tasks in WP 4

- Task 1: Development of evidence levels for small population groups
  - Task Leader: MUW
- Task 2: AD for confirmatory model based decisions
  - Task Leader: MUW; Partner: RUB, PWR
- Task 3: AD to enable omparative effectiveness
  - Task Leader: MUW; Partner: UKA, CTH

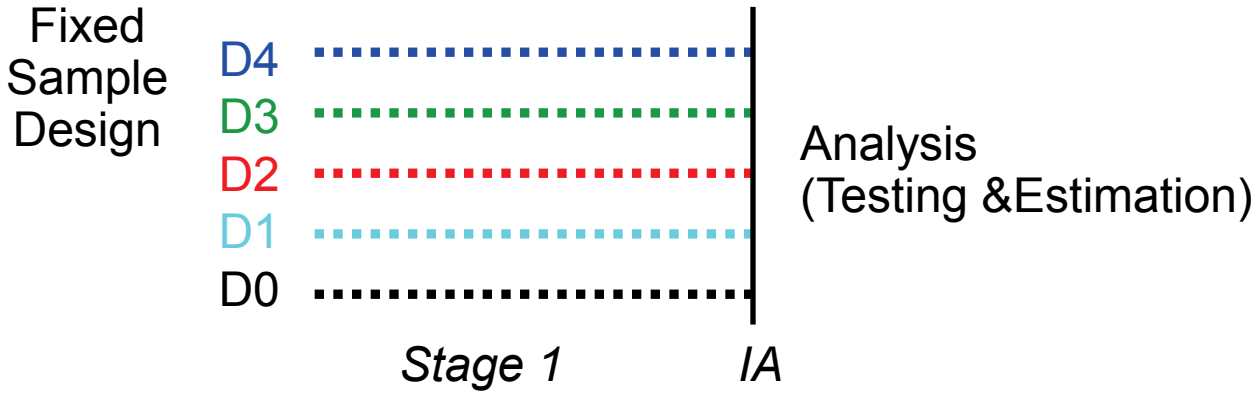
T1: Development of evidence levels for SPGs

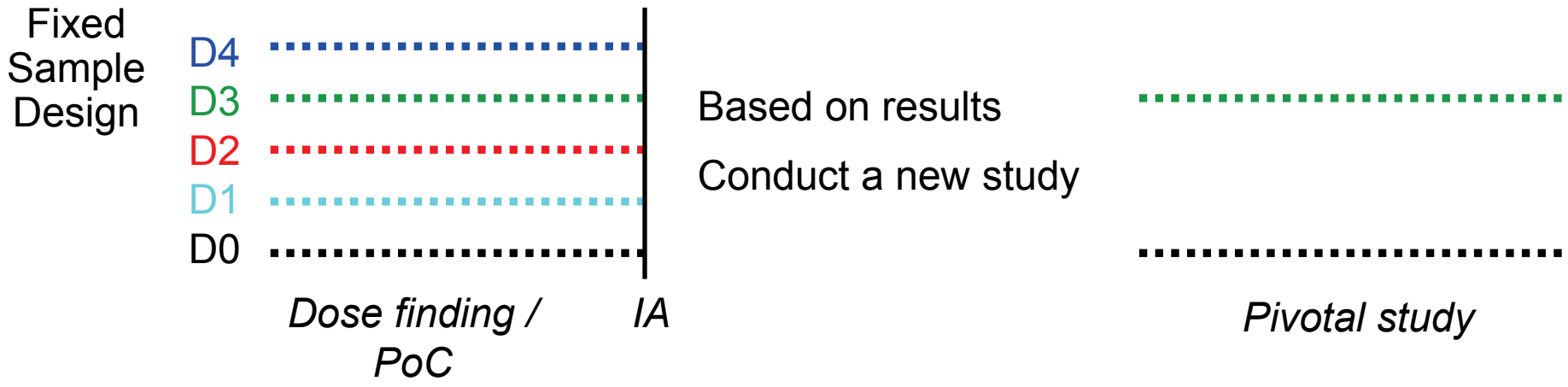
- Full development programme not feasible
- Use prior knowledge for inference in SPGs
- Studies conducted in related (larger) populations and/or similar drug substances basis for (partly) extrapolating efficacy and safety
- Depending on similarity →
  - adapt either the required level of evidence, sample sizes and/or testing strategy for SPGs
- Link between Bayesian methods and classical frequentist decision making criteria

T2: AD for confirmatory model based decision

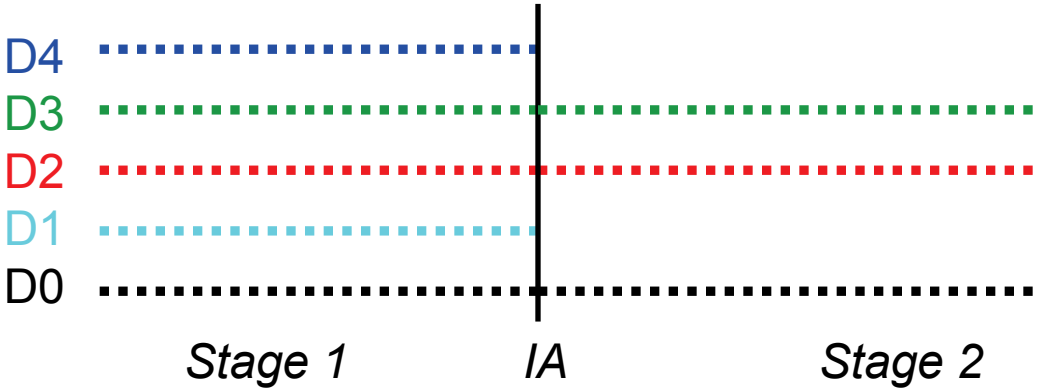
- Adaptive clinical trials …
  - to perform efficient dose finding at an adaptive interim analysis (IA)
  - to confirmatory demonstrate efficacy using all accumulated data (before and after the IA)

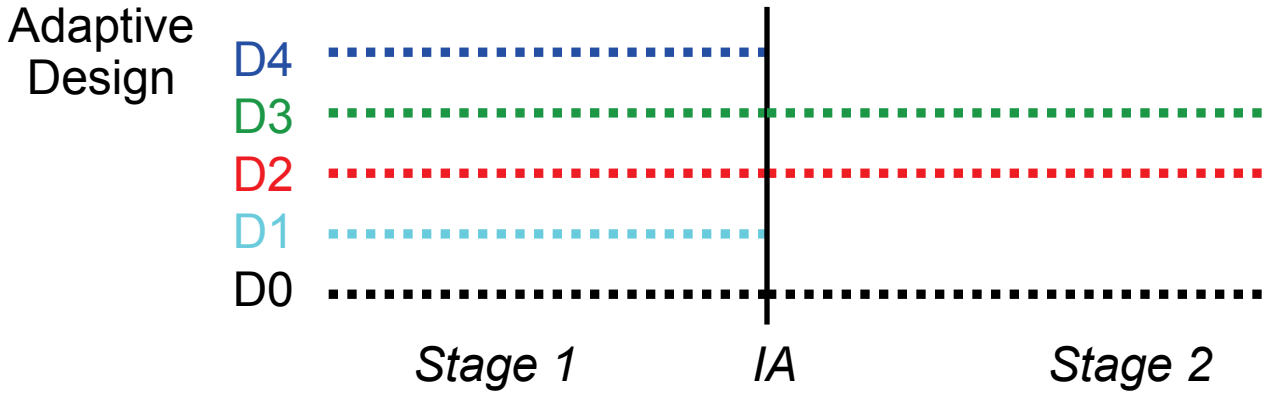
- Final decision based on
  - Clinically relevant endpoint
  - And/or appropriate surrogate parameters


Fixed
Sample
Design
D4
D3
D2
D1
D0
Analysis
(Testing &Estimation)
Stage 1
IA

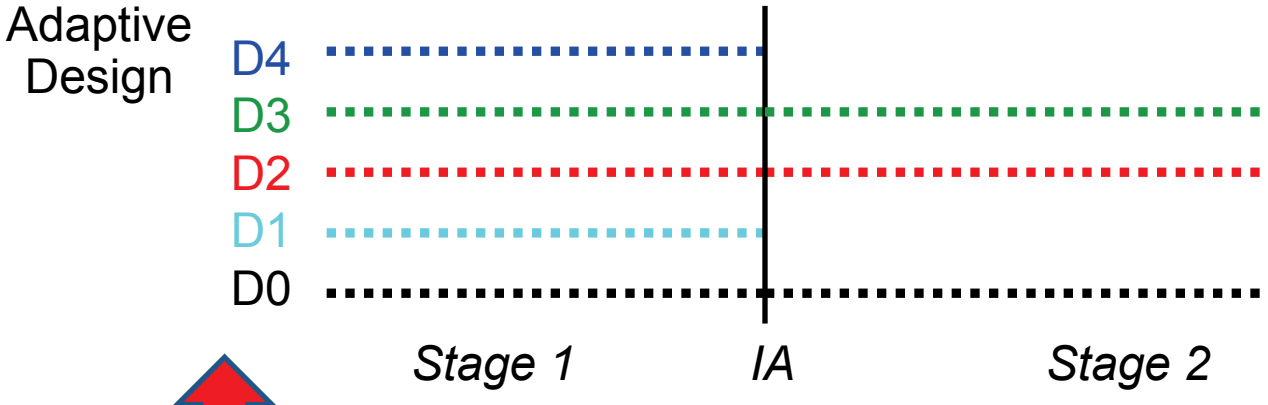

Fixed Sample Design
D4
D3
D2
D1
D0
Dose finding / PoC
IA
Based on results
Conduct a new study
Pivotal study

Adaptive Design

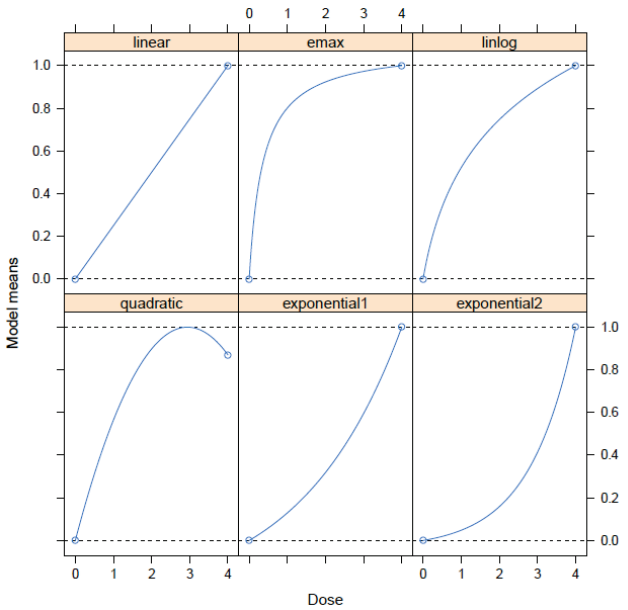


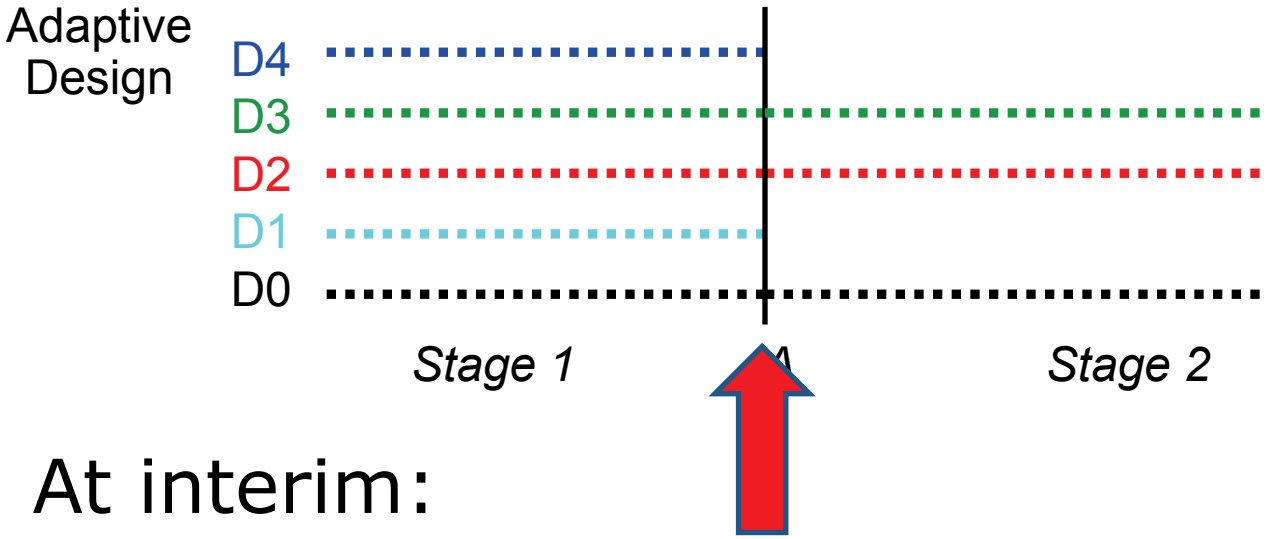


- We would like to use testing & modeling
- But how to deal with uncertainity concering specifying the right model?
- MCPMod (Bretz et al. 2004, Bretz et al. 2008, Bjornkamp et al. 2009)

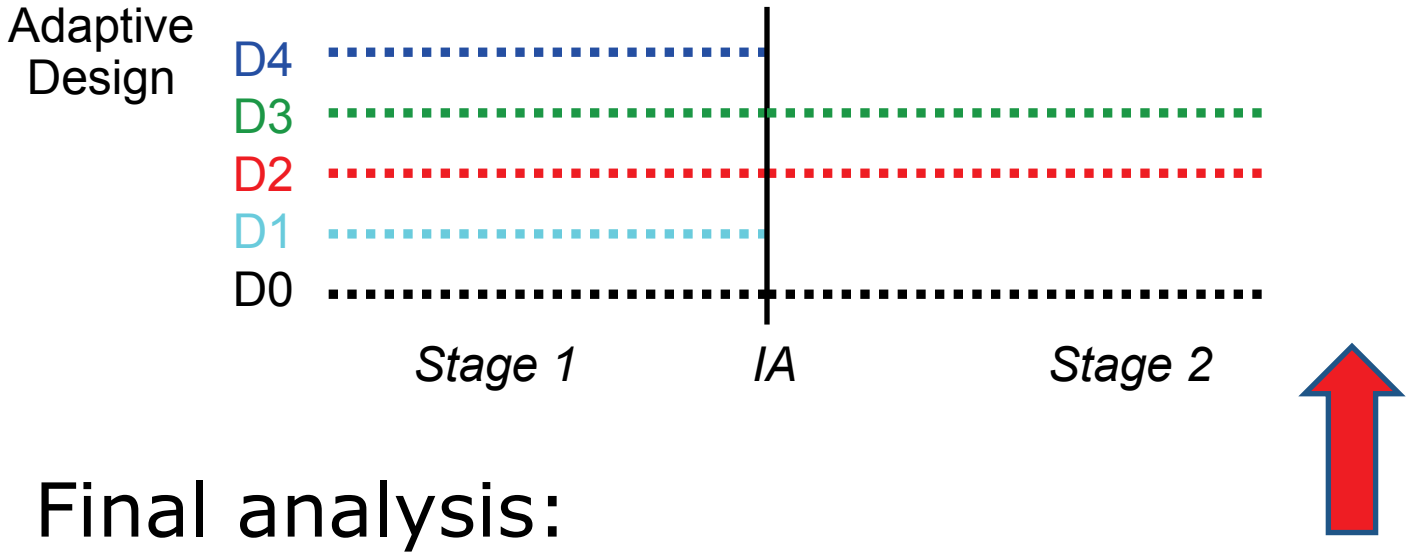


- # Before trial starts:
  - Fix the design of the first stage (sample sizes, doses groups, ...)
  - and candidate models for the first stage.





- At interim:
  - Fix the design of the second stage (adapt sample sizes, selection of doses, ...) and candidate models (drop/add models,refine parameter guesses).
  - Use the modeling part of MCPMod to support interim decisions (e.g., estimate MED or highest dose in a range ...)



- Final analysis:
  - Test PoC and/or elementary null hypotheses (for a single dose) using data from stage I + II with stage-wise trend tests.
  - Combine MCPMod, Adaptive Combination Tests and Closed Testing Principle to achieve type I error control

T3: AD to enable comparative effectiveness analysis

- How to address the different needs of regulators and reimbursers?
- Gold-standard: three arm trials (**E**xperimental, **P**lacebo, **A**ctive Comparator)
- Which available sample sizes allow which designs?

- Two-stage AD to drop or reduce sample size of placebo
- Response AD (with WP2): shift emphasis from **E-P** to the comparison **E-A** if evidence of efficacy of N becomes more and more promising

What shall be delivered by IDEAL?

What shall be delivered by all IDEAL WPs?

- Papers in statistical journals
- Review papers
- Free software code (in R) & manual, e.g., to assess operating charactersistics of proposed adaptive designs
- Shortcourses, e.g., on adaptive designs
- Online survey to assess status-quo in 2014:
  - involving all important stakeholders
- Regular meetings
  - Open symposium on small population, 1-2 July 2014, Vienna
  - Investigator meeting in November 2014, Paris

- Input to regulatory guidance documents (see next slide)

Input to Regulatory Guidance Documents

- IDEAL sent comments to EMA on
  - 'Draft guideline on adjustment for baseline covariates' (EMA/295050/2013)
  - MCP-Mod as an efficient statistical methodology for model-based design and analysis of phase II dose finding studies under model uncertainty.
- Next steps:
  - Draft EMA Guideline on the investigation of subgroups in confirmatory clinical trials
  - Reflection Paper on "Extrapolation of efficacy and safety in medicine development"

Plans for collaboration with DIA ADSWG

INTERACTION with DIA

- Link between DIA ADSWG and IDEAL
  - Carl-Fredrik (chair of DIA ADSWG AP and member in DIA ADSWG)
  - Franz (in ADSWG and DIA ADSWG and DIA Working Group „Small Populations“)
- Joint research projects
- Input to IDEAL Online-Survey

Symposium on small populations, 1-2 July

- Symposium on Small Populations
  1st and 2nd of July 2014
  Vienna, Austria

- Joint symposium of three FP7 projects on small populations

- Includes post-conference short courses on
  - Surrogate marker evaluation in clinical trials
  - Randomisation in clinical trials
  - Adaptive Clinical Trial Designs

- Visit symposium webpage at
  http://statistics.msi.meduniwien.ac.at/hp/small2014/

Symposium on small populations

Objectives of the joint symposia:

- To inform about the research plans of the three FP7 projects
- To facilitate the collaboration between FP7-projects and interaction with external stakeholders including EU FP7 representative, patient organizations, regulatory agencies, industry, ethics committee, …)
- To discuss status-quo of methodological issues in small populations research
- To discuss proposals for new and improved statistical design methodologies for clinical trials
- To train young researchers in this topic

- WE WOULD BE GLAD IF YOU COULD COME!

HOW TO STAY IN CONTACT WITH IDEAL

- VISIT THE IDEAL WEBPAGE
  - http://www.ideal.rwth-aachen.de
- Get LinkedIn IDEAL – FP7 Project
  - http://www.linkedin.com/groups/IDEAL-FP7-Project-6556030
- Twitter @ideal_fp7
  - https://twitter.com/ideal_fp7

Many thanks for your patience!

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