Overview on IDeAl
Integrated DEsign and AnaLysis of small population group trials

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with Malgorzata Bogdan, Carl-Fredrik Burman, Holger Dette, Mats Karlson, Franz König, Christoph Male, France Mentre, Geert Molenberghs, Stephen Senn

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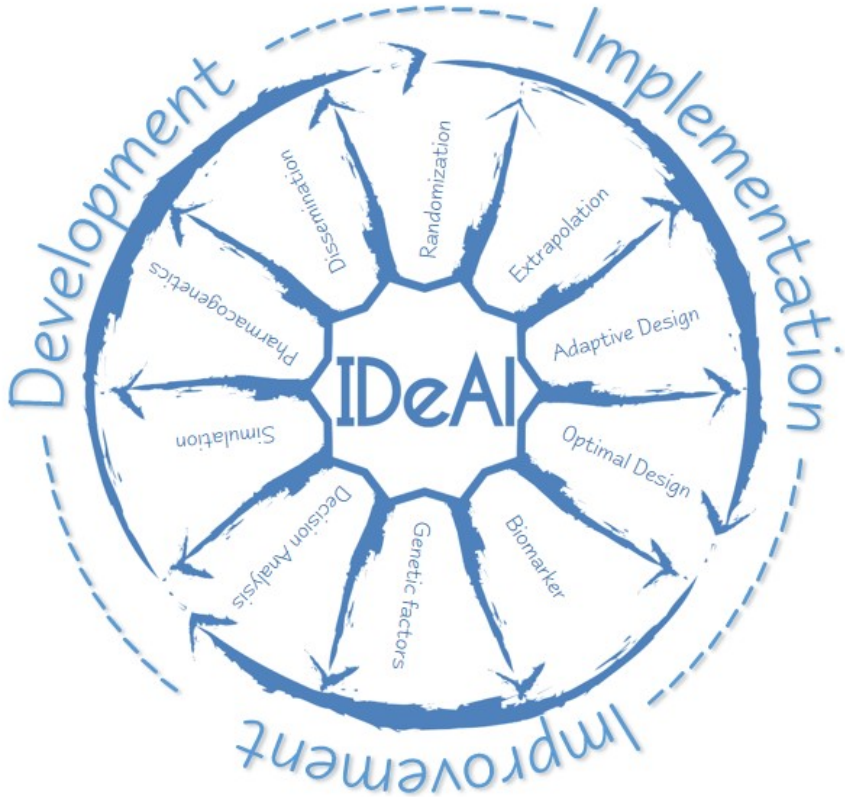
Table of contents

IDeAI Mission

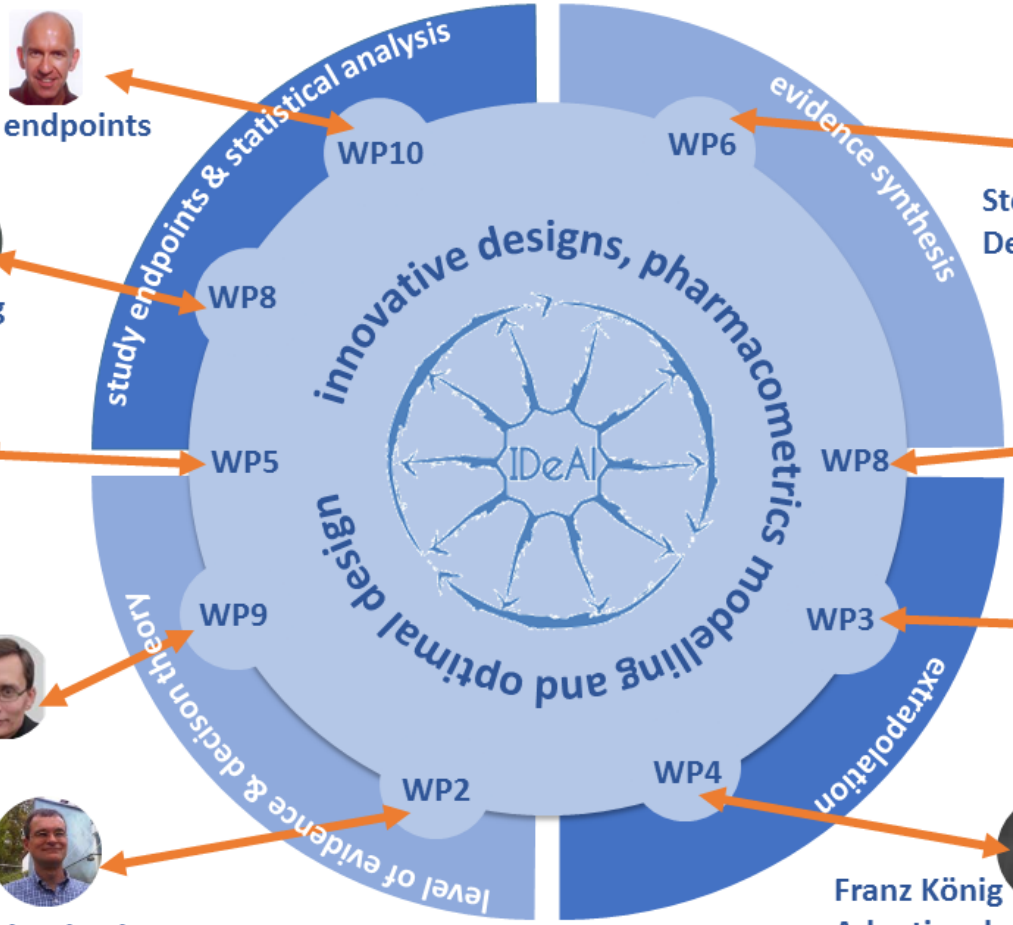
aims to refine the statistical methodology for clinical trials in small population groups by strictly following the concept of an improved integration of design, conduct and analysis of clinical trials from various perspectives.



IDeAI Work Program

1. **WP 2:** Assessment of randomisation procedures and randomisation based tests in SPG
2. **WP 3:** Extrapolating dose response information to SPG
3. **WP 4:** Adaptive design studies in SPG
4. **WP 5:** Optimal design in mixed models to analyse studies in SPG
5. **WP 6:** Design of pharmacogenetic SPG trials, incl. cross-over trials, n-of-1 trials and enrichment trials
6. **WP 7:** Simulation of clinical trials in SPG
7. **WP 8:** Genetic factors influencing the response to the therapy in SPG
8. **WP 9:** Decision analysis in SPG
9. **WP 10:** Biomarker surrogate endpoints in SPG
10. **WP 11:** Dissemination

Structure of the IDeAI Project



Geert Molenberghs
Biomarker surrogate endpoints

Malgorzata Bogdan
Genetic factors influencing response to therapy

France Mentré
Optimal design in mixed models

Carl-Fredrik Burman
Decision analysis

Ralf-Dieter Hilgers
Assessment of randomization

Stephen Senn
Design of pharmacogenetic trials

Mats Karlsson
Simulation of clinical trials

Holge Dette
Extrapolating dose response information

Franz König
Adaptive design studies

Setting up the Scene

- Relating the project to CHMP guideline
  (ref: Hilgers 2015 (∪ asterix + InSPiRe))
- First Recommendations
  (ref: Hilgers 2016, Jonker 2016 (∪ asterix + InSPiRe))
- Bridging to Big Data in Healthcare
  (ref: Auffray 2016 (∪ asterix))
- 25 Years adaptive designs
  (ref: Bauer 2016)
- Applications
  (ref: Reetz 2016, Rübben 2016)

IDeAI contribution to *Evidence synthesis*

- How to deal with potential heterogeneity in evidence synthesis / meta-analysis of small population clinical trials
  (ref: Senn 2014)
- New approaches to include historical controls and/or prior clinical trial data into design and analysis of small population trials
  (ref: Eichler 2016 (∪ asterix))
- Sharing clinical trial data
  (ref: König 2014 (∪ asterix + InSPiRe))

- *additional aspects:*
  Interpretation of p-values (ref: Greenland 2015).

Extrapolation

- Extrapolation of dose response information: Design and Analysis
  (ref: Dette 2016, Schorning 2016)
- Adapting the significance level for clinical trials in vulnerable, small populations, based on prior evidence of larger populations
  (ref: Hlavin 2016 (∪ asterix))
- Confirmatory design and analysis allowing adaptive design modifications, such as selection of a more promising subgroup
  (ref: Graf 2014b (∪ asterix), Klinglmueller 2014)

- *additional aspects:*
  Adaptive paediatric investigation plan (ref: Bauer 2016)

Level of Evidence and Decision Theoretic Aspects

- Value, performance and implications of different randomization methods in small size trials
  (ref: Tamm 2014, Kennes 2015, Rückbeil 2017, Uschner 2017)
- Decision-theoretic and value-of-information models (taking patient horizon into account) for clinical trials in small populations
- Decision theoretic approaches for targeted therapies with special focus on societal in contrast to commercial sponsor's perspective
  (ref: *Burman 2014*, **Jobjörnsson 2016)**
- Adapting the usual level of evidence
  (ref: Hlavin 2016 (∪ asterix))

- *additional aspects:*
  Analysis of R&D productivity (ref: Lendrem 2015)

Study Endpoints and Statistical Analysis

- Improving value and potentially efficiency (statistically and in terms of recruitment) of trials with patient centric outcomes
- Surrogate endpoints: Assessing, validation
  (ref: Alonso 2015a, 2016, vdElst 2015, 2016a,b)
- Leveraging multiple endpoints in small trial size setting
  (ref: Klinglmueller 2014)

- *additional aspects:*
  reliability models using LMEM, (ref: vdElst 2016c)
  randomization based inference in LMEM, (ref: Burger 2014)
  Validating predictors (ref: Alonso 2015b, 2017, Bogdan 2015)
  Identification of genetic factors (ref: Lee 2016, Bogdan 2015)
  Observations below limit of detection (ref: Berger xx)

Innovative designs, Pharmacometrics, modelling and optimal designs

- Multi-armed trial, with adaptive features, in small populations
  (ref: Graf 2014a)
- PtC for N-of-1 trials, Cross over trials,
  (ref: Araujo 2016, Senn 2015, Gewandter 2016,)
- Pharmacometrical modelling and design considerations of NLMEM
  (ref: Riviere 2016, Ueckert 2016, Deng 2016, Dosne 2016a,b, Strömberg 2017)
- Optimal sequential designs and sample size reassessment in small populations (with large prior uncertainty)
  (ref: Magirr 2016 (∪ asterix))
- Dose-finding including PK and dose limiting toxicities
- *additional aspects:* PoC study (ref: Gewandter 2014)
  Discussion of problems with first-in-human studies (ref: Bird 2017)
  Designs for target therapies (ref: Ondra 2017 (∪ InSPiRe), Senn 2017)

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External Advisory Board

No	Name	Country
1	Segolene Aymé	(F)
2	Rosemary Bailey	(UK)
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8	Chris Jennison	(UK)

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12	Gérard Pons	(F)
13	William F. Rosenberger	(USA)
14	Chiara Sabati	(USA)
15	Günther Schmalzing	(D)
16	Gernot Wassmer	(D)

actually **11 publications** with coauthorship of EABs

IDeAI Output

- 50 publications in peer reviewed journals (current state)
- released various freely available software programms (R packages)
- regular newsletters
- presentations at various conferences
  (among other: FDA, IRDiRC, MALTAEU2017(COMP, IMI, EURORDIS,..))
- organized conferences, sessions and workshops at conferences,
- webinar series available via website
- input to regulatory guidelines
- study stays abroad program
- input to design and analysis of rare disease clinical trials

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asterix, IDeAI, InSPiRe - Network

- close contact to Kit Roes (asterix) and Nigel Stallard (InSPiRe)
- IRDiRC task force on small population clinical trials
- joint publications (**9/50**)
- develop a synthesis statement of the three funded projects
- contribution to review of CHMP Small Population Guideline

Keep in touch with IDeAI

- VISIT THE IDeAI WEBPAGE
  - http://www.ideal.rwth-aachen.de
- Get LinkedIn IDEAL ? FP7 Project
  - http://www.linkedin.com/groups/IDEAL-FP7-Project-6556030
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