IDeAl Webinar Series 2016
WP11 Dissemination

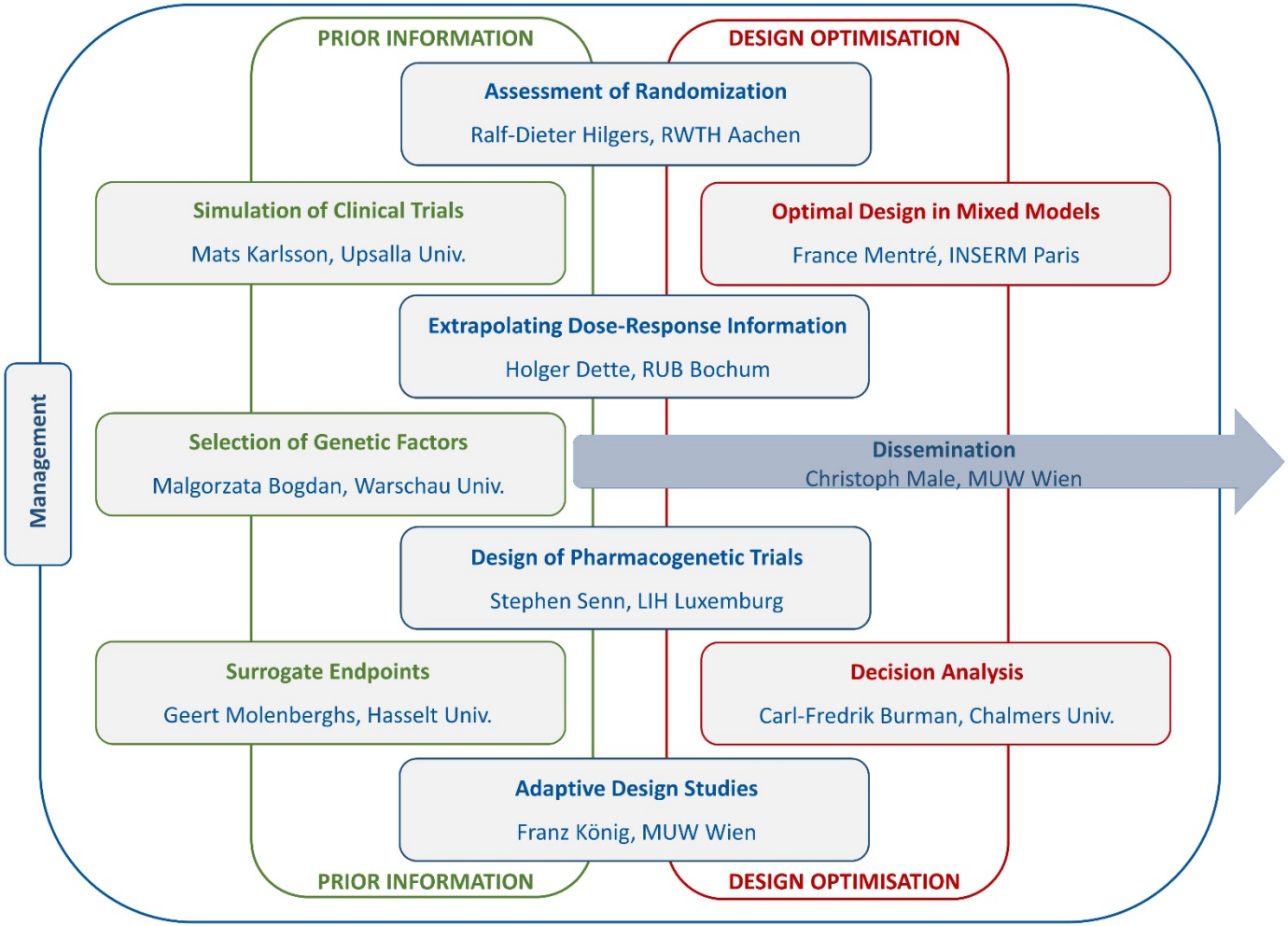
2016-11-17

R.-D. Hilgers, C. Male and F. König

rhilgers@ukaachen.de franz.koenig@meduniwien.ac.at

This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration grant agreement no: 602552.

We have reached the final webinar in our series



Most important …

Next year there will be a **joint Workshop** on small populations to present the main results of **all three FP7 funded projects** at the **European Medicines Agency**

asterix

Integrated DEsign and AnaLysis of small population group trials

InSPiRe
Innovative methodology for small populations research

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Joint Workshop 2017

- Joint workshop at European Medicines Agency (EMA) together with other FP7 projects ASTERIX and Inspire

- Steering Committee
  - EMA coordination: R. Herold
  - FP7 Project Chairs: RD Hilgers (IDeAl), K. Roes (asterix), N. Stallard (InSPiRe)
  - N. Benda, S. Day, A. Koch, F. Koenig, C. Male, M. Posch, F. Torres

- Duration: 1.5 days
- Venue: EMA (London, UK)
- Proposed date: March, 2017
- Participants: Researchers from the three FP7 projects, advisory boards, regulators, patient representatives, clinicians, industry, CROs, academia, methodological researchers in small populations field, ...

Joint Workshop 2017

Topics to be discussed will include

- Level of evidence and decision theoretic aspects
- Extrapolation
- Study Endpoints
- Innovative Designs
- Modelling and optimal Designs [Pharmacometrics]
- Evidence Synthesis

- **More details** will be published in the **next IDeAl newsletter!**

Newsletter

- Mailing list contains >300 subscribers

- So far 6 newsletter:
  - September 2014, December 2014
  - August 2015, December 2015
  - July 2016, September 2016: Announcement of the Webinar series

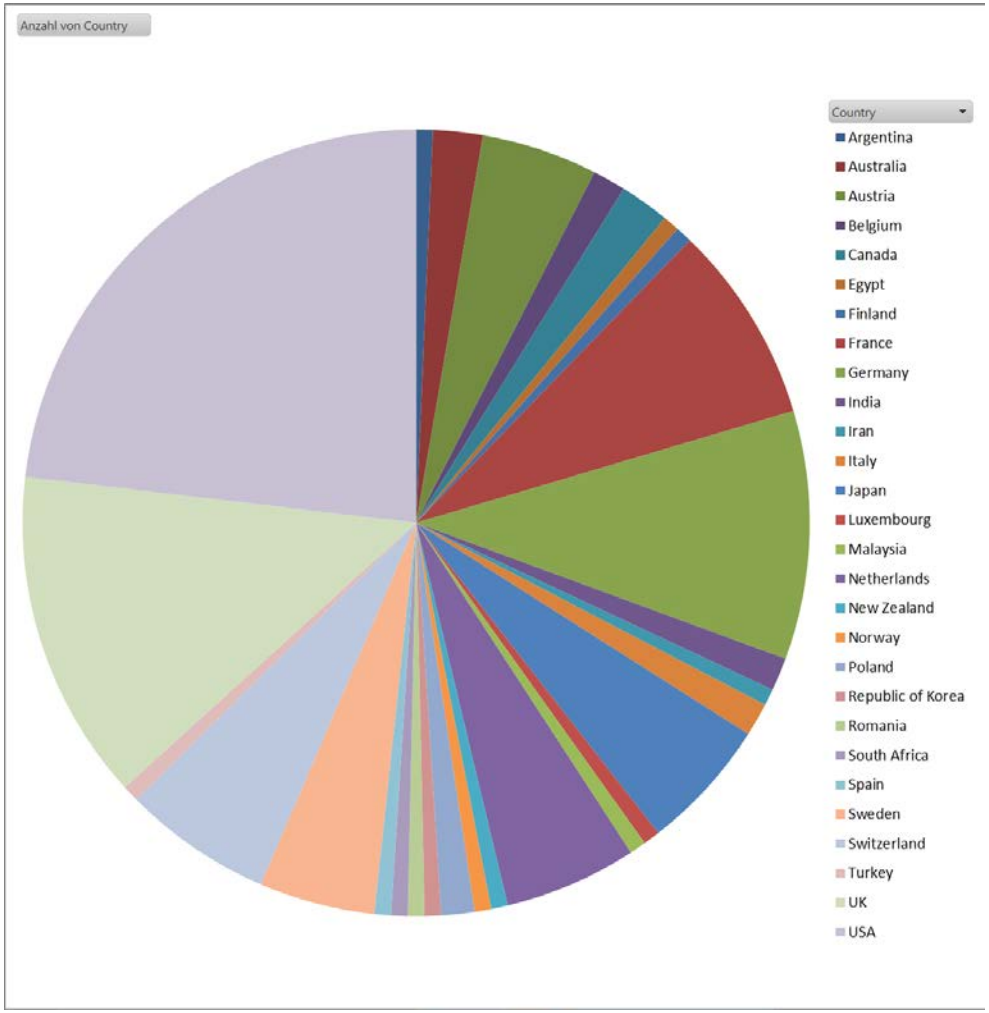
- Due to the prolongation we will have 2 more newsletters
  - End of 2016 (Dec 2016)
  - End of project (April 2017)

Subscribe to newsletter at
http://www.ideal.rwth-aachen.de/?page_id=989

Many thanks to our editors Gerald Hlavin and Diane Uschner!

Who is interested in our work?

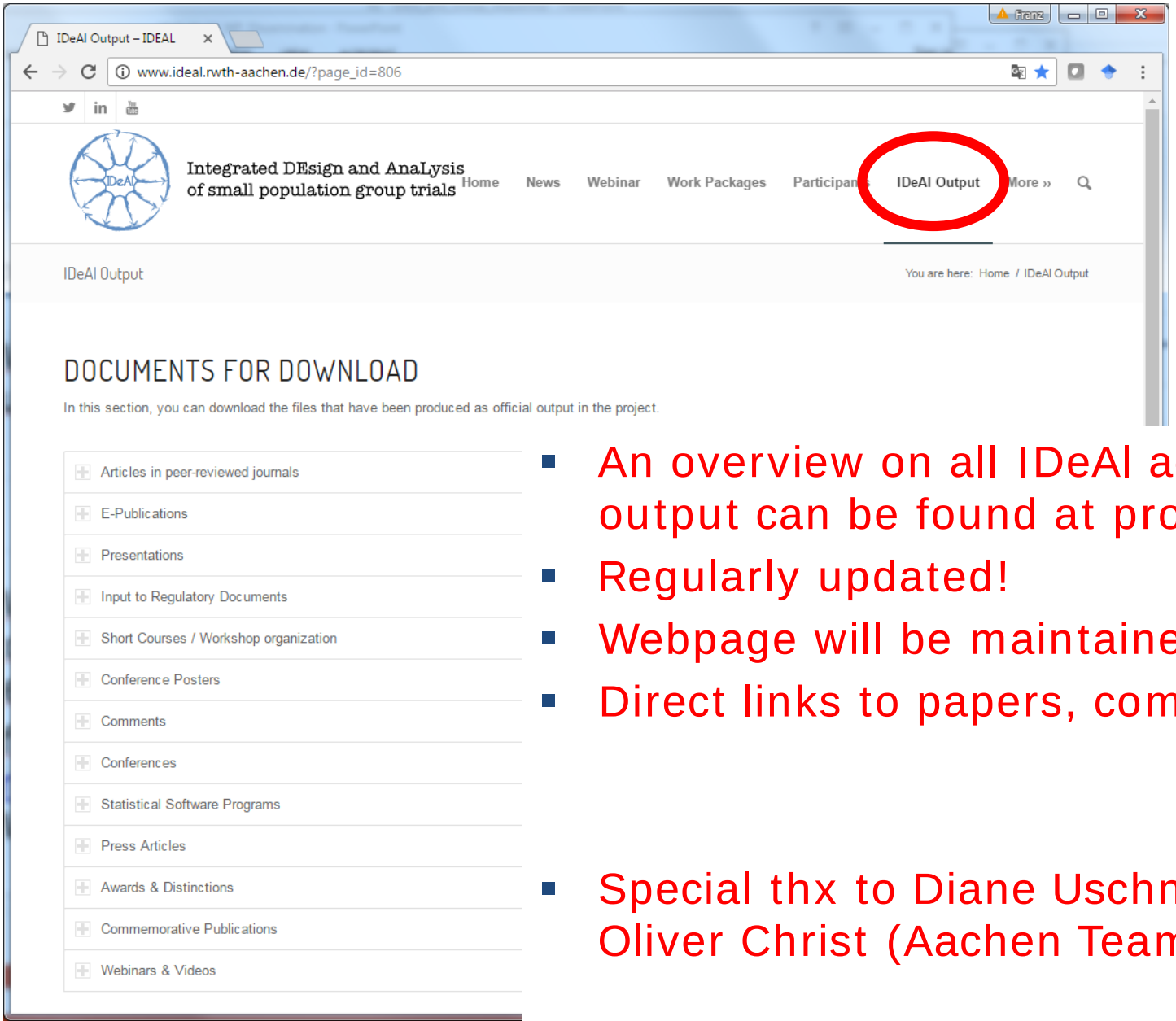
Distribution of registrations by countries (before Webinars)
Newsletter registrations … still people register!)



Important Dissemination Activities

- **Webpage**
- External Advisory Board (EAB)
- Young Scientist
- Newsletter
- **Publications**
- **Software**
- Presentations (conferences, among other also at regulatory agencies EMA, FDA & PMDA)
- Workshops / short courses / tutorials at various conferences
- Webinars (**IDeAl Webinar Series**, KOL, ASA, PSI-RSS, ...)
- Organisation of conferences and sessions at conferences
- Collaborations
- Study stays abroad program
- Blog posts on statistical methods
- Press Releases
- Social media (Twitter, LinkedIn)

Visit our IDeAl webpage at http://www.ideal.rwth-aachen.de/



- An overview on all IDeAl activities and output can be found at project webpage
- Regularly updated!
- Webpage will be maintained till 2020
- Direct links to papers, comments, etc

- Special thx to Diane Uschner und Oliver Christ (Aachen Team)

Publications

- # published
  - 40 publications in peer review journals
  - Many open access
  - Link to papers on IDeAl webpage
  - Widespread topics (range from new methods till applications)
- # review articles
  - 6 review articles
- # E-pub
  - 5 publications on preprint-servers (e.g. arxiv.org)
- And some more submitted / working paper

Review Paper (5+1)

Published:

Gewandter, J.et al. **Reporting of cross-over clinical trials of analgesic treatments for chronic pain: ACTTION systematic review and recommendations.** PAIN 2016.

Hilgers, RD et al. **Directions for new developments on statistical design and analysis of small population group trials.** Orphanet Journal of Rare Diseases. 2016

Auffray, C et al. **Making sense of big data in health research: Towards an European Union action plan. Genome Medicine.** 2016.

Bauer, P et al.**Twenty-five years of confirmatory adaptive designs: opportunities and pitfalls.** Statistics in Medicine, 2016

Gewandter, J.Set al. **Research designs for proof-of-concept chronic pain clinical trials: IMMPACT recommendations.** Pain. 2014

Submitted:

Hilgers, RD, et al. Design and Analysis of Clinical Trials for Small Rare Disease Populations, Submitted 2016.

Milestone – Software

R packages / Software Code / Shiny Applications

- … for optimization of Bayesian decision problems
- … for genome-wide association studies with SLOPE
- … for testing similarity of dose response curves
- … on randomization for clinical trials
- … “MIXFIM” for the evaluation and optimization of the Fisher information matrix in non linear mixed effect models
- … for the estimation of within subject correlations based on linear mixed effects models
- … on the prediction of therapeutic success … for dimensionality reduction via variables clustering
- … on surrogate markers
- … to determine significance level when extrapolating from a source (e.g. adult) to a targeted population (e.g. children)
- R application for joint genotype and admixture mapping in admixed populations
- R-Code to calculate maximum type I error inflation in multiarmed clinical trials
- …

Short-Courses / Tailored Training Programs

- Several short courses (1/2, full, 2 days, …) on topics such as …
  - Adaptive Designs, N-of-1-trials, Randomisation and Stratification, Surrogate Markers, Longitudinal and incomplete data, Dose finding, Statistical Issues in Drug Development, Extrapolation, …

- We are happy to offer further short courses / webinar trainings on IDeAl related topics on request.

- If you are interested, please contact

  rhilgers@ukaachen.de or franz.koenig@meduniwien.ac.at

  or the WP-leader of a particular work package concerned

Upcoming Short Courses with IDeAl contribution

- Tutorial "**Regulatory statistics with some European perspectives**" and 2 day course "**Adaptive designs and multiple testing**", 72nd Deming Conference on Applied Statistics. December 5-9, 2016 at Atlantic City, New Jersey.

- Course "**Adaptive Designs**", Nov 24, Graz, Austria.

Organisation of Conferences / Seminar

- **1.5 day Workshop with IDeAl, Asterix and Inspire at EMA in March (tbc) 2017**

- Joint Seminar with IBS-WBS and Asterix, Nov 2016
- **Design and Analysis of Experiments in Healthcare**. 6-10 July, 2015. Isaac Newton Institute, Cambridge, UK
- Joint WBS-Winterseminar on **Innovative Statistical Approaches in Drug Development**, Dec 2014
- Joint Symposium on Small Populations (Asterix, IDeAl and Inspire), 1-3 July,2014, Vienna

Further selected events

- Invited Pannel Session „**Frontiers of Confirmatory Inference in Small Populations.** F König. 02. September 2015. 9th International Conference on Multiple Comparison Procedures in Hyderabad, India.MCP2015
- Contribution to Joint Workshop on **Small Population Clinical Trials Challenges in the Field of Rare Diseases** organized by **IRDiRC-EMA** Small Population Clinical Trials Task Force. 2016

Further Outreach Activities - Networking

- Close contact to Kit Roes (**Asterix**) and Nigel Stallard (**InSPiRe**)
  - Presentations at Novartis (10/2015), MRC Workshop London (12/2015)

- **IRDiRC** task force on small population clinical trials
  - Workshop 3/2016
  - Small Population Clinical Trials Task Force Workshop Report and Recommendations June 2016
  - paper in preparation

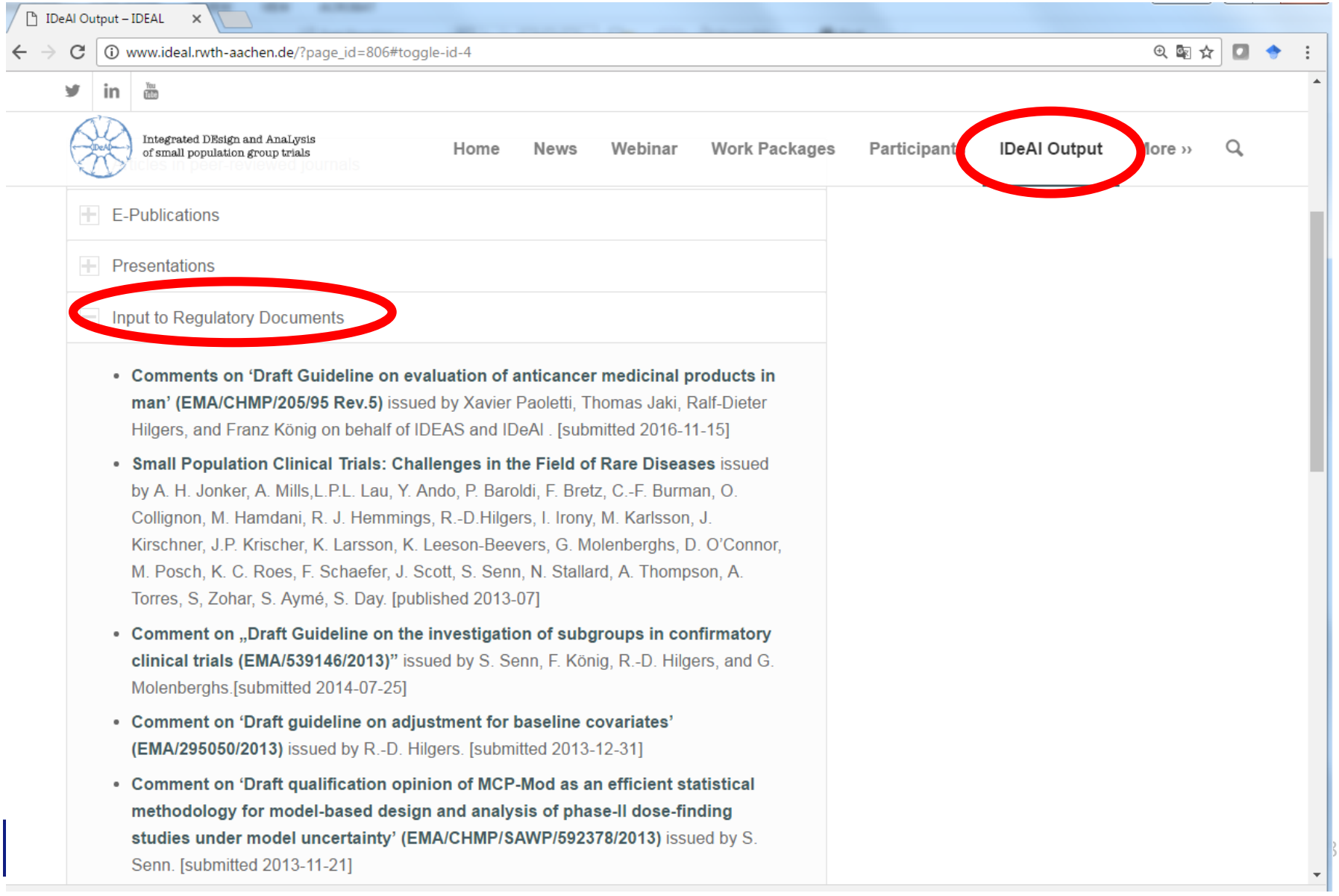
- **European Medicines Agency** (EMA)
  - EAB (special thx to Ralf Herold)
  - Joint collaborations

Milestone: Input to Regulatory Guidance Documents

- Contribution to discussion at EMA
- Input to guidelines
  - EMA/295050/2013 (Guideline on adjustment for baseline covariates)
  - EMA/CHMP/SAWP/592378/2013 (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/539146/2013 (Guideline on the investigation of subgroups in confirmatory clinical trials)
  - EMA/424858/2016 (Developing a framework of collaboration between the European Medicines Agency (EMA) and academia)
  - EMA/CHMP/205/95 Rev.5 (Guideline on evaluation of anticancer medicinal products in man)

- Input to EMA/129698/2012 (Concept paper on extrapolation of efficacy and safety in medicine development)

IDeAl webpage www.ideal.rwth-aachen.de -> IdeAl – Output -> Comments



ID
->

.rwth-aachen.de
nents

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 July 2014

Submission of comments on '<Guideline on the investigation of subgroups in confirmatory clinical trials>' (EMA/539146/2013)

Comments from:

Name of organisation or individual
Stephen Senn, Franz of the IDEAL team (ID Framework Programr demonstration under aachen.de/) (Contact

Please note that these cor
justified objection is receiv

When completed, this forn
format (not PDF).

General Remark

Also according to the EMA
[*] should be accessible vi
wondering why for the mo
(adaptive designs, multipli
the comments sent to EMA
by EMA) have not been pu
and how the comments ha
statistical guidelines.

[*]
http://www.ema.europa.e
p&mid=WC0b01ac058002

7 Westferry Circus • Canary Whar
Telephone +44 (0)20 7418 8400
E-mail info@ema.europa.eu **Web**

Torres, S, Zo

- **Comment o**
  clinical trial
  Molenberghs
- **Comment o**
  (EMA/29505
- **Comment o**
  methodolog
  studies und
  Senn. [subm

Webinar Work Packages Participants IDeAI Output More ››

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	Although this draft guideline[1] makes many interesting points there are a number that are controversial and even some that do not appear to be well thought-out. This is no doubt a reflection of the fact that this difficult field is one for which methodologists are still struggling to agree rational recommendations. Of course this is an unsatisfactory situation but it raises the question as to whether a guideline of this sort is not premature. Although one may feel that it is better to have some guidance than none, the danger is that ill thought-out recommendations become frozen as standard practice. Our general feeling is that this guideline needs to go back for major revision and that it may need face-to-face meetings between regulators, sponsor and other interested parties to come to a sensible conclusion.	
	The guideline as a whole risks allowing 'the best to become the enemy of the good' (to use a phrase employed by Klim McPherson in another context[2]). If a treatment has convincingly shown that it is superior to control *on average* then although it is true that this does not prove that it is superior to control for every subgroup, it is irrational to prefer to continue to use the control for that reason since there are no grounds at all for believing that the control is better for every subgroup. Therefore, it is a mistake to take the point of view that it is necessary for the sponsor to demonstrate efficacy in key subgroups. The guideline needs to recognise that some values needs to be placed on the inferentially conservative position that in the absence of	

ID
-> aachen.de

25 July 2014

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Submission of
investigation o
(EMA/539146/

Comments from

Name of organisation or in

Stephen Senn, Franz
of the IDEAL team (ID
Framework Programm
demonstration under
aachen.de/) (Contact

*Please note that these co
justified objection is recei*

*When completed, this forn
format (not PDF).*

General Remark

Also according to the EMA
[*] should be accessible vi
wondering why for the mo
(adaptive designs, multipli
the comments sent to EMA
by EMA) have not been pu
and how the comments ha
statistical guidelines.

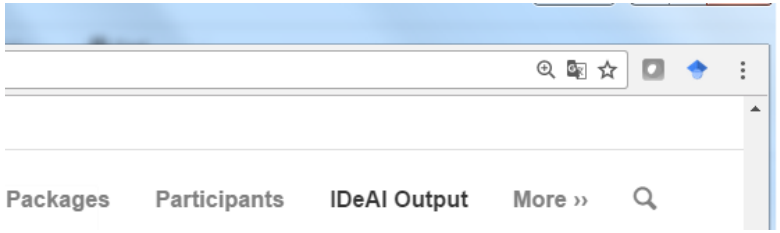
[*]
http://www.ema.europa.e
p&mid=WC0b01ac058002

7 Westferry Circus • Canary Whar
Telephone +44 (0)20 7418 8400
E-mail info@ema.europa.eu Web

Torres, S, Zo

- Comment o
clinical trial
Molenbergh
- Comment o
(EMA/29505
- Comment o
methodolog
studies und
Senn. [subm

Submission of comments on 'Draft Guideline on evaluation of anticancer medicinal products in man' (EMA/CHMP/205/95 Rev.5)



Comments from:

Name of organisation or individual
Xavier Paoletti (Gustave Roussy), Thomas Jaki (Lancaster University), Ralf-Dieter Hilgers (RTWH Aachen) and Franz König (Medical University of Vienna)* on behalf of the **IDEAS** (This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 63356, see http://www.ideas-itn.eu/) and **IDeAI** (IDEAL is a research project funded by the European Union's 7th Framework Programme for research, technological development and demonstration under grant agreement no. 602552, http:// * correspondence to franz.koen Disclaimer: The views and opini any organisation with which the

*Please note that these commen
justified objection is received.*

*When completed, this form sho
format (not PDF).*

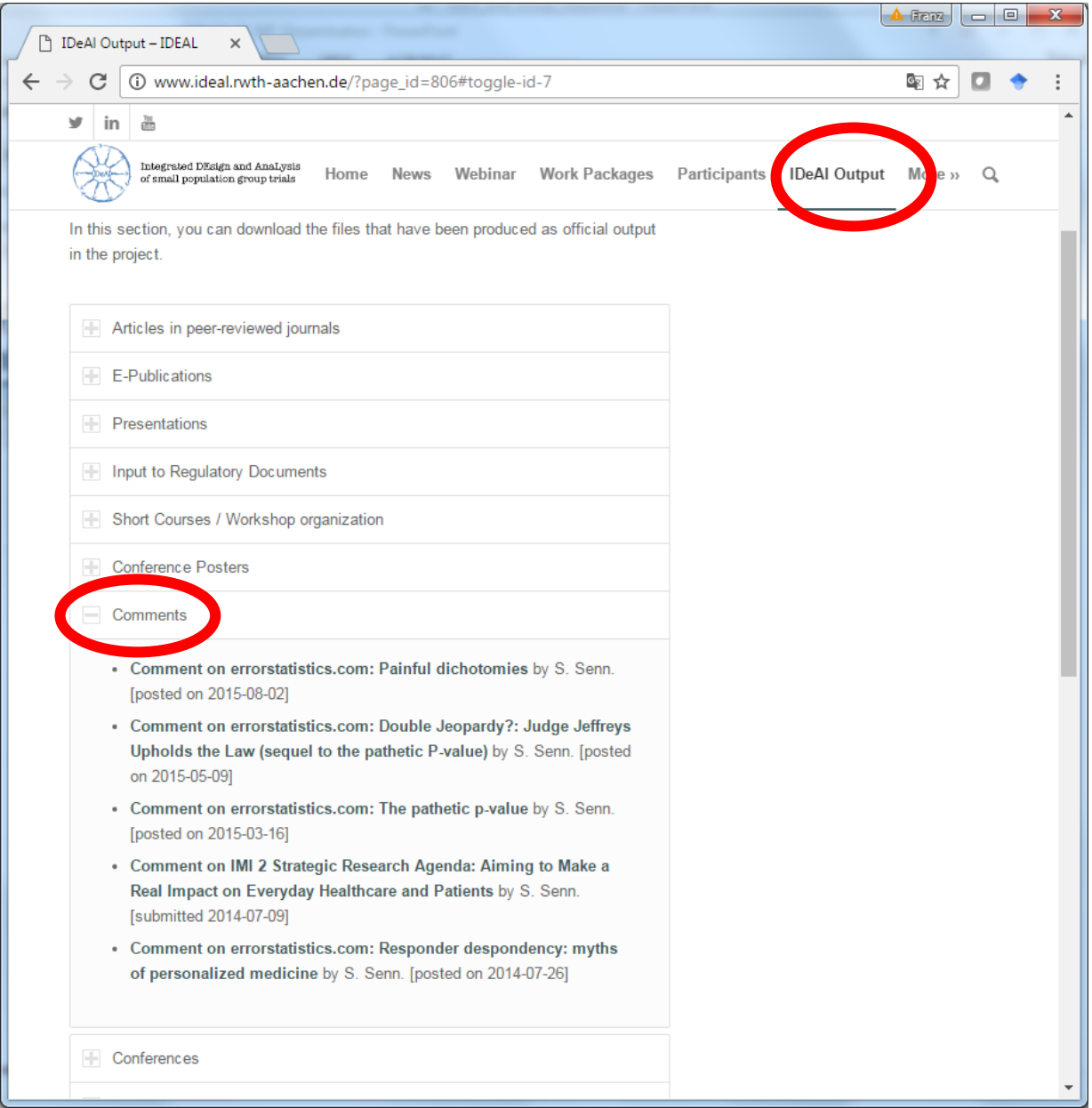
30 Churchill Place • Canary Wharf • Lond
Telephone +44 (0)20 3660 6000 Facsi
Send a question via our website www.e

© European Medicines Ag

Outcome (if applicable) *(To be completed by the Agency)*

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		been demonstrated to be predictive of the response to treatment.	
L841onwards		Comment: Within the IDeAl project it could be shown, that randomization does not protect against bias in general. According to the ICH E9 guideline, the potential impact of bias on the study results should be investigated. Consequently the selection of the randomization procedure which best protect against bias in the particular study setting, should be based on scientific arguments by conduct of a scientific comparative evaluation study. The IDeAl project has developed the software and framework for this evaluations study. Proposed Changes: In blue text in section 7.1.4. ("Randomisation and blinding": Randomisation and stratification should adhere to the general principles laid down in current guidelines (CPMP/ICH/363/96). **The selection of a particular randomization procedure should be based on scientific arguments, taking into account the clinical trial setting as well as the resulting impact of bias on the study results.** In many cases, a double-blind design is no option due to obvious differences in toxicity between study regimens or due to safety concerns. If the study has to be conducted open label, this has implications with respect to choice of **the randomization procedure,** study endpoints, independent review, conduct of	

IDeAI webpage www.ideal.rwth-aachen.de -> IdeAI – Output -> Comments



Young Scientists

- IDeAl Young Scientists and Young Scientists from Asterix and IDeAl
  - Held regular formal and informal meetings at IDeAl meetings and conferences
  - Disseminated research among themselves and in their partner institutions
  - Constructed a network of young biostatisticians in industry, regulators offices and academia
  - Will spread the IDeAl methodology at their future work places.

PhD‘s and Careers

- **Damian Brzyski** defended his Doctoral Thesis in 2016, now Postdoc position at the Fairbanks School of Public Health of Indiana University (Bloomington, USA)
- **Sebastion Jobjörnsson** defended his Licentiate Thesis in 2016.
- **Miriam Tamm** defended her Doctoral Thesis in 2015, now works as a biostatistician at Bayer, Wuppertal, Germany.
- **Nicole Heussen** was offered a professorship in biostatistics at Sigmund Freud University Vienna (2016)
- **Wim van der Elst** 2016, now works as senior biostatistician at Janssen
- **Kristin Karlsson** 2016, now at the Swedish Medical Products Agency, Uppsala, Sweden
- **Chenhui Deng** 2016, now Pfizer Research & Development, Shanghai, China
- **Olivier Collignon** seconded to the European Medicines Agency (ongoing)
- **Marie Karelle Riviere**, now biostatistician in methodology (Sanofi, France)
- **David Schindler** submitted his thesis (September 2016)
- **G Hlavin, S Krasnozhon, and D Uschner** are currently finishing their PhDs
- **G Hlavin new job at Austrian “Hauptverband”** in section responsible for reimbursement of drugs (similar to NICE in UK or IQWIG in Germany)

How to stay in contact …

- **Visit the IDeAl WEBPAGE**
  http://www.ideal.rwth-aachen.de

- **On LinkedIn**
  http://www.linkedin.com/groups/IDEAL-FP7-Project-6556030

- **Follow us on Twitter @ideal fp7**
  https://twitter.com/ideal fp7

- **Per Email**
  rhilgers@ukaachen.de or franz.koenig@meduniwien.ac.at

Who we are – IDeAl Meeting Nov 2016

Many thanks …

… to all researchers and organisations having been involved in the IDeAl project for the last three years

WP-leaders:
Bogdan, Malgorzata, PWR
Burman, Carl-Fredrik, CTH
Dette, Holger, RUB
Haas, Eva, RWTH, DE
Heussen, Nicole, UKA
Hilgers, Ralf-Dieter, UKA, Project Coordinator/Chair
König, Franz, MUW
Karlsson, Mats, UU
Male, Christoph, MUW
Mentré, France, INSERM
Molenberghs, Geert, UHASSELT
Senn, Stephen, CRP-SANTE

External Advisory Board

N°	Name	City
1	Segolene Aymé	Paris (F)
2	Rosemary Bailey	St Andrews (UK)
3	Paolo Baroldi	Washington (USA)
4	Frank Bretz	Basel (CH)
5	Tomasz Burzykowski	Cambridge (USA)
6	Martin Forster	Heslington (UK)
7	Ralf Herold	(UK)
8	Chris Jennison	Bath (GB)

N°	Name	City
9	Steven A. Julious	Sheffield (GB)
10	Gerard Nguyen	Bobigny (F)
11	Paolo Pertile	Verona (I)
12	Gérard Pons	Paris (F)
13	William F. Rosenberger	Fairfax (USA)
14	Chiara Sabati	Stanford (USA)
15	Günther Schmalzing	Aachen (D)
16	Gernot Wassmer	Cologne (D)

Near Future

- Selected topics were presented in the webinar our developments over 3 years
- more results can be found in the papers
- more results will be published in the next month (-> website)

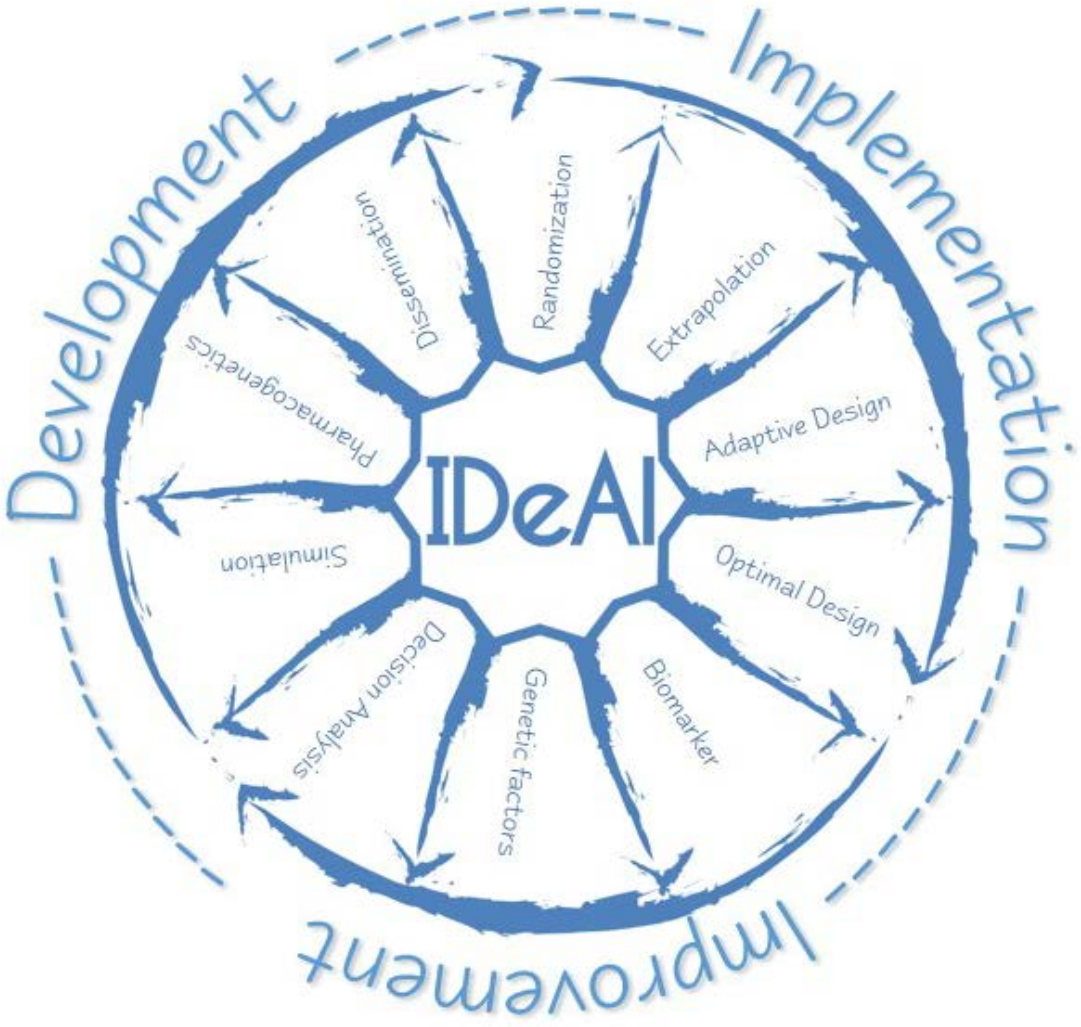
- Major Step will be the joint meeting at EMA

If you missed one of the IDeAl Webinar Series

- 11 Webinars (with participants from all over the world including people from US and Japan!)
- Available on Youtube http://www.ideal.rwth-aachen.de/?page_id=1732

Date	Presenter	Title
4. Oct	Ralf-Dieter Hilgers	The IDeAl webinar series - introduction
6. Oct	Ralf-Dieter Hilgers	Selection of a randomization procedure Does it matter? How it works!
11. Oct	Mats Karlsson	A sampling importance resampling procedure for estimating parameter uncertainty
13. Oct	Holger Dette	Statistical inference for comparing small population groups
18. Oct	Geert Molenberghs	Pseudo-likelihood and split-sample methods in small and very large studies (FP7-IDEAL / ExaScience)
20. Oct	Franz König	Adaptive level of evidence
25. Oct	Stephen Senn	A little bit me, a little bit you: N of 1 trials, random effects and shrinkage estimators
27. Oct	France Mentré	Using Hamiltonian Monte Carlo to design clinical trials with longitudinal data
10. Nov	Malgorzata Bogdan	Identifying genetic factors influencing important patient's characteristics
15. Nov	Carl-Fredrik Burman	Optimal decisions and stakeholder interactions
17. Nov	Christoph Male Franz König	Dissemination

Thank you for your interest!



This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration grant agreement no: 602552.