Opportunities for academia to collaborate on and receive funding for regulatory science research

Franz König and Martin Posch
Center for Medical Statistics, Informatics and Intelligent Systems
franz.koenig@meduniwien.ac.at
https://cemsiis.meduniwien.ac.at/user/koenig-franz/

Methodological topics relevant for regulatory science?

- Identifying and tackling problems relevant for drug development and regulatory decision making
  - adaptive designs, multiplicity, estimands, extrapolation, master protocols, …
- Developing methods and designs complying with current regulatory standard and guidelines
- Contributing to evolving regulatory standards (scientific papers, guidelines, advices, …)
- Applying new methodology in clinical trials

Regulatory science

Who is interested in regulatory topics?

- Regulators,
- HTAs,
- Pharmaceutical industry
- CROs
- Patients and public
- Trial sponsors
- Ethics committees

Who will fund regulatory topics?

- Public funding
  - Local (national) funding
  - Cross-countries funding
  - European funding programs (FPx programs, H2020, IMI, ..)
  - …
- Industry funding
- …

Types of support and funding

- Research projects,
- PhD grants,
- PostDocs,
- interships,
- research visits,
- access to data,
- …

Some History of Adaptive Designs

1989	Bauer: “Multistage Testing with Adaptive Designs”
1995	Proschan & Hunsberger: “Designed Extension of Studies Based on Conditional Power”
2007	EMA Reflection Paper
2010	FDA Draft Guidance (Drugs and Biologics)
2015	FDA Draft Guidance (Devices, CDRH, CBER) - finalized 2017
2018	New FDA Draft Guidance (Drugs and Biologics) – finalized 2019
2019	Concept paper ICH E20 Adaptive Clincal Trials

Featured Article

Statistics in Medicine

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(wileyonlinelibrary.com) DOI: 10.1002/sim.6472

Twenty-five years of confirmatory adaptive designs: opportunities and pitfalls

Peter Bauer,[a] Frank Bretz,[b,c] Vladimir Dragalin,[d] Franz König[a] and Gernot Wassmer[e,f*†]

http://dx.doi.org/10.1002/sim.6472 (Open Access)

With invited discussion by Hung, Wang and Lawrence; Mehta and Liu; Vollmar; Maurer

Some History of A

1989	Bauer: "M
1995	Proschan Condition
2007	EMA Refle
2010	FDA Draft
2015	FDA Draft
2018	New FDA
2019	Concept p

Elsäßer et al. Trials 2014, 15:383
http://www.trialsjournal.com/content/15/1/383

TRIALS

RESEARCH Open Access

Adaptive clinical trial designs for European marketing authorization: a survey of scientific advice letters from the European Medicines Agency

Amelie Elsäßer[1], Jan Regnstrom[2], Thorsten Vetter[2], Franz Koenig[3], Robert James Hemmings[4], Martina Greco[2], Marisa Papaluca-Amati[2] and Martin Posch[3*]

Abstract

Background: Since the first methodological publications on adaptive study design approaches in the 1990s, the application of these approaches in drug development has raised increasing interest among academia, industry and regulators. The European Medicines Agency (EMA) as well as the Food and Drug Administration (FDA) have published guidance documents addressing the potentials and limitations of adaptive designs in the regulatory context. Since there is limited experience in the implementation and interpretation of adaptive clinical trials, early interaction with regulators is recommended. The EMA offers such interactions through scientific advice and protocol assistance procedures.

Methods: We performed a text search of scientific advice letters issued between 1 January 2007 and 8 May 2012 that contained relevant key terms. Letters containing questions related to adaptive clinical trials in phases II or III were selected for further analysis. From the selected letters, important characteristics of the proposed design and it context in the drug development program, as well as the responses of the Committee for Human Medicinal Products (CHMP)/Scientific Advice Working Party (SAWP), were extracted and categorized. For 41 more recent procedures (1 January 2009 to 8 May 2012), additional details of the trial design and the CHMP/SAWP responses were assessed. In addition, case studies are presented as examples.

Results: Over a range of 5½ years, 59 scientific advices were identified that address adaptive study designs in phas II and phase III clinical trials. Almost all were proposed as confirmatory phase III or phase II/III studies. The most frequently proposed adaptation was sample size reassessment, followed by dropping of treatment arms and population enrichment. While 12 (20%) of the 59 proposals for an adaptive clinical trial were not accepted, the great majority of proposals were accepted (15, 25%) or conditionally accepted (32, 54%). In the more recent 41 procedures, the most frequent concerns raised by CHMP/SAWP were insufficient justifications of the adaptation strategy, type I error rate control and bias.

Conclusions: For the majority of proposed adaptive clinical trials, an overall positive opinion was given albeit with critical comments. Type I error rate control, bias and the justification of the design are common issues raised by th CHMP/SAWP.

Keywords: adaptive design, EMA, FDA, seamless designs, scientific advice, clinical trials, phase II-III, pivotal trial, orphan drugs

* Correspondence: Martin.Posch@meduniwien.ac.at
[3]Center for Medical Statistics, Informatics and Intelligent Systems, Medical University of Vienna, Spitalgasse 23, 1090 Vienna, Austria
Full list of author information is available at the end of the article

Collignon et al. Trials (2018) 19:642
https://doi.org/10.1186/s13063-018-3012-x

Trials

RESEARCH Open Access

Adaptive designs in clinical trials: from scientific advice to marketing authorisation to the European Medicine Agency

Olivier Collignon[1,2*], Franz Koenig[3], Armin Koch[4], Robert James Hemmings[5], Frank Pétavy[1], Agnès Saint-Raymond[1], Marisa Papaluca-Amati[1] and Martin Posch[3]

Abstract

Background: In recent years, experience on the application of adaptive designs in confirmatory clinical trials has accumulated. Although planning such trials comes at the cost of additional operational complexity, adaptive designs offer the benefit of flexibility to update trial design and objectives as data accrue. In 2007, the European Medicines Agency (EMA) provided guidance on confirmatory clinical trials with adaptive (or flexible) designs. In order to better understand how adaptive trials are implemented in practice and how they may impact medicine approval within the EMA centralised procedure, we followed on 59 medicines for which an adaptive clinical trial had been submitted to the EMA Scientific Advice (SA) and analysed previously in a dedicated EMA survey of scientific advice letters. We scrutinized in particular the submission of the corresponding medicines for a marketing authorisation application (MAA). We also discuss the current regulatory perspective as regards the implementation of adaptive designs in confirmatory clinical trials.

Methods: Using the internal EMA MAA database, the AdisInsight database and related trial registries, we analysed how many of these 59 trials actually started, the completion status, results, the time to trial start, the adaptive elements finally implemented after SA, their possible influence on the success of the trial and corresponding product approval.

Results: Overall 31 trials out of 59 (53%) were retrieved. Thirty of them (97%) have been started and 23 (74%) concluded. Nine of these trials (39% out of 23) demonstrated a significant treatment effect on their primary endpoint and 4 (17% out of 23) supported a marketing authorisation (MA). An additional two trials were stopped using pre-defined criteria for futility, efficiently identifying trials on which further resources should not be spent. Median time to trial start after SA letter was given by EMA was 5 months. In the investigated trial registries, at least 18 trial (58% of 31 retrieved trials) designs were implemented with adaptive elements, which were predominantly dose selection, sample size reassessment (SSR) and stopping for futility (SFF). Among the 11 completed trials including adaptive elements, 6 demonstrated a significant treatment effect on their primary endpoint (55%).

(Continued on next page)

Secondments to EMA enabled analysis on how adaptive design methodologies are used in drug development programs!

* Correspondence: olivier.collignon@ema.europa.eu; olivier.collignon@lih.lu
[1]European Medicines Agency, 30 Churchill Place, London E14 5EU, UK
[2]Competence Center for Methodology and Statistics, Luxembourg Institute of Health, 1A-B, rue Thomas Edison, L-1445 Strassen, Luxembourg
Full list of author information is available at the end of the article

How was the research on adaptive designs initially funded at our department

- **National funding:** Austria Science Fund FWF
  - **Standalone projects** to fund mainly PhDs and Post-Docs, e.g. FP15853-N04 "Evaluation of Adaptive Design Procedures“, P18698-N15 "Adaptive Designs - Evaluation and New Applications“, P23167 Hypothesis Testing and Estimation in Adaptive Designs with Blinded and Unblinded Interim Analysis"
  - **Mobility programs** (especially of interest for early stage researcher)
    - FWF Erwin Schrödinger Programs, e.g Nr. J 3721 "Permutation Tests for Adaptive Clinical Trials“ (F. Klinglmüller)
- **Cross-countries funding (to facilitate research visits, joint workshops,** …
  - FWF and JSPS (Japan Society for the Promotion of Science): Joint Seminar "Innovative Clinical Trial Designs for Accelerating Medical Product Development“ (with involvement of Japanese regularors PMDA)
  - Academic Research Collaboration Optimal Adaptive Trials with Treatment Selection" (British Council)
- **European funding** (examples on next slides)

At the end we want to report the results of adaptive RCTs as well …

- International consortium to develop an extension of the CONSORT Statement specifically for adaptive designs
- Grants by NIHR Clinical Trials Unit (CTU) Support Funding (NIHR129671) and MRC Network of HTMR (MR/L004933/1-R/N/P/B1)NIHR and MRC, https://www.sheffield.ac.uk/scharr/research/centres/ctru/ace, PI Dr Dimairo)
- Invitation to regulators to become members in the core group
- Broader invitation to participate in DELPHI-process when developing the guideline
- Sufficient budget foreseen to allow travelling of international collaborators

RESEARCH METHODS AND REPORTING

thebmj

The Adaptive designs CONSORT Extension (ACE) statement: a checklist with explanation and elaboration guideline for reporting randomised trials that use an adaptive design

Munyaradzi Dimairo,[1] Philip Pallmann,[2] James Wason,[3,4] Susan Todd,[5] Thomas Jaki,[6] Steven A Julious,[1] Adrian P Mander,[2,3] Christopher J Weir,[7] Franz Koenig,[8] Marc K Walton,[9] Jon P Nicholl,[1] Elizabeth Coates,[1] Katie Biggs,[1] Toshimitsu Hamasaki,[10] Michael A Proschan,[11] John A Scott,[12] Yuki Ando,[13] Daniel Hind,[1] Douglas G Altman,[14] on behalf of the ACE Consensus Group

For numbered affiliations see end of the article.

Correspondence to: M Dimairo m.dimairo@sheffield.ac.uk; mdimairo@gmail.com (ORCID 0000-0002-9311-6920)

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Adaptive designs (ADs) allow pre-planned changes to an ongoing trial without compromising the validity of conclusions and it is essential to distinguish pre-planned from unplanned changes that may also occur. The reporting of ADs in randomised trials is inconsistent and needs improving. Incompletely reported AD randomised trials are difficult to reproduce and are hard to interpret and synthesise. This consequently hampers their ability to inform practice as well as future research and contributes to research waste. Better transparency and adequate reporting will enable the potential benefits of ADs to be realised.

This extension to the Consolidated Standards Of Reporting Trials (CONSORT) 2010 statement was developed to enhance the reporting of randomised AD clinical trials. We developed an Adaptive designs CONSORT Extension (ACE) guideline through a two-stage Delphi process with input from multidisciplinary key stakeholders in clinical trials research in the public and private sectors from 21 countries, followed by a consensus meeting. Members of the CONSORT Group were involved during the development process.

The paper presents the ACE checklists for AD randomised trial reports and abstracts, as well as an explanation with examples to aid the application of the guideline. The ACE checklist comprises seven new items, nine modified items, six unchanged items for which additional explanatory text clarifies further considerations for ADs, and 20 unchanged items not

The intention is to enhance transparency and improve reporting of AD randomised trials to improve the interpretability of their results and reproducibility of their methods, results and inference. We also hope indirectly to facilitate the much-needed knowledge transfer of innovative trial designs to maximise their potential benefits.

"To maximise the benefit to society, you need to not just do research but do it well" *Douglas G Altman*

Purpose of the paper

Incomplete and poor reporting of randomised clinical trials makes trial findings difficult to interpret due to study methods, results, and inference that are not reproducible. This severely undermines the value of scientific research, obstructs robust evidence synthesis to inform practice and future research, and contributes to research waste.[1,2] The Consolidated Standards Of Reporting Trials (CONSORT) statement is a consensus-based reporting guidance framework that aims to promote and enhance transparent and adequate reporting of randomised trials.[3,4] Specific CONSORT extensions addressing the reporting needs for particular trial designs, hypotheses, and interventions have been developed.[5] The use of reporting guidelines is associated with improved completeness in study reporting[6-8]; however, mechanisms to improve adherence to reporting guidelines are needed.[9-12]

We developed an Adaptive designs CONSORT Extension (ACE)[13] to the CONSORT 2010 statement[3,4] to support reporting of randomised trials that use an adaptive design (AD)—referred to as AD randomised trials. In this paper, we define an AD and summarise some types of ADs as well as their use and reporting. We then describe briefly how the ACE guideline was developed, and present its scope and underlying principles. Finally, we present the ACE checklist with explanation and elaboration (E&E) to guide its use.

Adaptive designs: definition, current use, and reporting

The ACE Steering Committee[13] agreed a definition of an AD (box 1) consistent with the literature.[14-18]

Boosters for regulatory research and collaboration among relevant stakeholders

- Dedicated conferences or (panel) sessions organized by learned socities, e.g.,
  - Workshop of joint working on adaptive designs of IBS ROeS and German Region, MCP, DIA European regulatory workshop, ..
- EMA workshops on regulatory statistics topics such as adaptive designs (2006, 2009), multiplicity, extrapolation, small populations (2017), single arm trials (2016) ….
- Plans to issue/revise an EMA concept paper, guideline, …
- Research visits (university secondments to EMA or industry, interships, …)
- Working group of learned socities (DIA, ASA, PSI, EFSPI, IBS ROeS and German Region, ...)
- … and dedicated EU calls on topics of regulatory interests

3 EU FP7 Projects to enhance statistical methodology in SMALL POPULATIONS

asterix

FP7 HEALTH 2013 – 602144
http://www.asterix-fp7.eu/

Advances in Small Trials dEsign for Regulatory Innovation and eXcellence)

InSPiRe
Innovative methodology for small populations research

FP7 HEALTH 2013 – 603160
www.warwick.ac.uk/InSPiRe

IDeAL

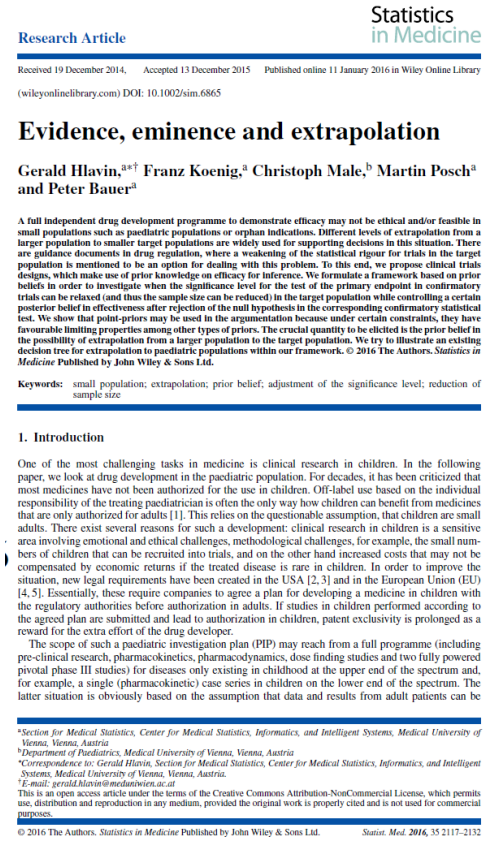
Integrated DEsign and AnaLysis of small population group trials
FP7 HEALTH 2013 – 602552
http://www.ideal.rwth-aachen.de/

- Dedicated call to enhance statistical methodology for small populations
- EMA hosted workshops, e.g., with IRDIC and a joint dissemination workshop of all three projects in 2017
- Joint paper by all projects
- Higher visibility compared to having separate workshops for each project
- Involvement of statisticians with regulatory experience
- Inclusion of learned societies
- Facilitated follow-up research call funded by EJP RD (https://www.ejprarediseases.org/)

Work on extrapolation

- Research involved researchers with regulatory background (members of PDCO)
- Research stimulated by discussion EMA concept paper on extrapolation
- Proposal on how to formalize how much evidence is needed for children
- Participation at workshops of EMA and other parties on extrapolation
- ICH E11A (start in 2017)

Integrated DEsign and AnaLysis of small population group trials



Research Article — Statistics in Medicine

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Evidence, eminence and extrapolation

Gerald Hlavin,[a*†] Franz Koenig,[a] Christoph Male,[b] Martin Posch[a] and Peter Bauer[a]

A full independent drug development programme to demonstrate efficacy may not be ethical and/or feasible in small populations such as paediatric populations or orphan indications. Different levels of extrapolation from a larger population to smaller target populations are widely used for supporting decisions in this situation. There are guidance documents in drug regulation, where a weakening of the statistical rigour for trials in the target population is mentioned to be an option for dealing with this problem. To this end, we propose clinical trials designs, which make use of prior knowledge on efficacy for inference. We formulate a framework based on prior beliefs in order to investigate when the significance level for the test of the primary endpoint in confirmatory trials can be relaxed (and thus the sample size can be reduced) in the target population while controlling a certain posterior belief in effectiveness after rejection of the null hypothesis in the corresponding confirmatory statistical test. We show that point-priors may be used in the argumentation because under certain constraints, they have favourable limiting properties among other types of priors. The crucial quantity to be elicited is the prior belief in the possibility of extrapolation from a larger population to the target population. We try to illustrate an existing decision tree for extrapolation to paediatric populations within our framework. © 2016 The Authors. *Statistics in Medicine* Published by John Wiley & Sons Ltd.

Keywords: small population; extrapolation; prior belief; adjustment of the significance level; reduction of sample size

1. Introduction

One of the most challenging tasks in medicine is clinical research in children. In the following paper, we look at drug development in the paediatric population. For decades, it has been criticized that most medicines have not been authorized for the use in children. Off-label use based on the individual responsibility of the treating paediatrician is often the only way how children can benefit from medicines that are only authorized for adults [1]. This relies on the questionable assumption, that children are small adults. There exist several reasons for such a development: clinical research in children is a sensitive area involving emotional and ethical challenges, methodological challenges, for example, the small numbers of children that can be recruited into trials, and on the other hand increased costs that may not be compensated by economic returns if the treated disease is rare in children. In order to improve the situation, new legal requirements have been created in the USA [2, 3] and in the European Union (EU) [4, 5]. Essentially, these require companies to agree a plan for developing a medicine in children with the regulatory authorities before authorization in adults. If studies in children performed according to the agreed plan are submitted and lead to authorization in children, patent exclusivity is prolonged as a reward for the extra effort of the drug developer.

The scope of such a paediatric investigation plan (PIP) may reach from a full programme (including pre-clinical research, pharmacokinetics, pharmacodynamics, dose finding studies and two fully powered pivotal phase III studies) for diseases only existing in childhood at the upper end of the spectrum and, for example, a single (pharmacokinetic) case series in children on the lower end of the spectrum. The latter situation is obviously based on the assumption that data and results from adult patients can be

[a]*Section for Medical Statistics, Center for Medical Statistics, Informatics, and Intelligent Systems, Medical University of Vienna, Vienna, Austria*
[b]*Department of Paediatrics, Medical University of Vienna, Vienna, Austria*
[*]*Correspondence to: Gerald Hlavin, Section for Medical Statistics, Center for Medical Statistics, Informatics, and Intelligent Systems, Medical University of Vienna, Vienna, Austria.*
[†]*E-mail: gerald.hlavin@meduniwien.ac.at*

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VIEWPOINT — Pharmaceutical Statistics

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Adaptive paediatric investigation plans, a small step to improve regulatory decision making in drug development for children?

Peter Bauer* and Franz König

Different arguments have been put forward why drug developers should commit themselves early for what they are planning to do for children. By EU regulation, paediatric investigation plans should be agreed on in early phases of drug development in adults. Here, extrapolation from adults to children is widely applied to reduce the burden and avoids unnecessary clinical trials in children, but early regulatory decisions on how far extrapolation can be used may be highly uncertain. Under special circumstances, the regulatory process should allow for *adaptive paediatric investigation plans* explicitly foreseeing a re-evaluation of the early decision based on the information accumulated later from adults or elsewhere. A small step towards adaptivity and learning from experience may improve the quality of regulatory decisions in particular with regard to how much information can be borrowed from adults. © 2016 The Authors. Pharmaceutical Statistics Published by John Wiley & Sons Ltd.

Keywords: paediatric medicine; adaptive; extrapolation; European regulation; clinical trials; drug development

Drug development in the paediatric population is one of the most sensitive areas in medicine involving various emotional, ethical and methodological challenges. For example, there may be only small numbers of children that can be recruited into studies but increased costs for drug developers which may not be compensated by economic returns especially if the disease is rare in children. Off-label drug use remains an important public health issue for infants, children and adolescents, because an overwhelming number of drugs still have no information in the labelling for use in paediatrics [1]. In 2007, a paediatric regulation (EU 1901/2006) [2] came into force in the EU also motivated by the impression that 'Market forces alone have proven insufficient to stimulate adequate research into, and the development and authorization of, medicinal products for the paediatric population' [2]. A key role in the new regulatory procedures has been taken over by a Paediatric Committee (PDCO) at the European Medicines Agency (EMA) which 'should be primarily responsible for the scientific assessment and agreement of paediatric investigation plans' (PIP). The new obligations are supplemented by a reward of a 6-months patent extension if all the measures included in the agreed PIP are complied with regard to timing with the EU regulation 'aims at ensuring that the development of medicinal products that are potentially to be used for the paediatric population becomes an integral part of the development of medicinal products, integrated into the development programme for adults. Thus, paediatric investigation plans should be submitted early during product development, …' [2] An early commitment of the applicant of his plans in children is asked for to avoid any delay of the paediatric development. Another advantage of an early development plan for children is that at this time it could be integrated scientifically in the adult development by planning studies in adults which in turn provide specific data relevant for the paediatric development. However, then, it would be reasonable to define later checkpoints to allow an assessment of the impact of evolving information on the planned paediatric development plan – possibly foreseeing the option of PIP adaptations.

A consequence of the paediatric regulation is that in general development programmes for children are laid down (and agreed on by the PDCO) early often when clinical data on efficacy in adults are still lacking. Here, we rely on our own experiences in the PDCO and EMA, respectively, and therefore focus on EU regulations. The scope of PIPs may reach from the one extreme of a full programme (including pre-clinical research, pharmacokinetics, pharmacodynamics, dose finding studies and two fully powered pivotal Phase III studies) for diseases only existing in childhood to the other extreme of, for example, only a single (pharmacokinetic) case series in children. In the EU regulation, it is stressed that the 'objectives should be achieved without subjecting the paediatric population to unnecessary clinical trials …: This is referring to the option of fully or partially extrapolating knowledge and data from adults to paediatric populations [3,4] which is an obvious and widely applied approach to reduce the burden of drug development in children [5]: for example, the PDCO may agree that a single study in children with a relaxed level of significance for demonstrating efficacy may be sufficient for market authorization [6], given a successful development in adults. The decision will be based on the nature of the drug and the disease and on

Center for Medical Statistics, Informatics, and Intelligent Systems, Medical University of Vienna, Vienna, Austria

**Correspondence to: Peter Bauer, Center for Medical Statistics, Informatics, and Intelligent Systems, Medical University of Vienna, Spitalgasse 23, 1090 Vienna, Austria.*
E-mail: peter.bauer@meduniwien.ac.at

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Marie Skłodowska-Curie Actions (MSCA)

5 types of MSCA targeting different objectives:

- **Doctoral Networks (DN)**
  Supporting programmes to train doctoral candidates in academic and non-academic organisations.
- **Postdoctoral Fellowships (PF)**
- **Staff Exchanges (SE)**
- **COFUND:** Co-funding of regional, national and international programmes
- **MSCA and Citizens**

- No topic specific calls
- Allows to tackle research questions as you wish!

Improving Design, Evaluation and Analysis of early drug development Studies

IDEAS
Improving drug development

http://www.ideas-etn.eu/

IDEAS was a European training network for early stage researchers working on statistical methods for early drug development. The network was funded by the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 633567 and comprised of 8 full partners and three associated partners at major European universities, the pharmaceutical industry, and consulting companies. (2015-18)

External advisory board including a CHMP member (Rob Hemmings)

1. Dose finding for combination trials with many treatments read more...
2. Pooling information on progression-free and overall survival in multi-arm cancer trials read more...
3. Using pre-clinical information to establish a safe dose in first-in-men studies read more...
4. Development of a biomarker score to identify a subgroup of treatment responders read more...
5. The impact of data and safety monitoring board decisions to drop treatments read more...
6. Optimal designs and analysis methods for the development of Biosimilars read more...
7. Predictive probability of success, as a criterion at clinical development milestones read more...
8. Innovative designs for combination of existing therapies read more...
9. Modelling and simulation for the early development of a modified administration route read more...
10. Bias and precision in early phase adaptive studies and its consequences for the decisions about conducting and designing confirmatory studies read more...
11. Interval estimation for dose-finding studies read more...
12. Statistical methods for phase I/II trials of molecularly targeted agents in oncology read more...
13. Statistical aspects of animal to human translation read more...
14. Detecting pharmacodynamic drug-drug interactions read more...

H2020 ITN IDEAS: subproject on biosimilars

EMA´s EPAR as starting point for the research to identify gaps. Involvement of former CAT member. Further interaction with other regulators at workshops such as http://biosimsforum.com/

British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2016) 82 1444–1457 1444

SYSTEMATIC REVIEW

Clinical trials for authorized biosimilars in the European Union: a systematic review

Correspondence Bernd Jilma, Department of Clinical Pharmacology, Medical University of Vienna, 1090 Vienna, Austria. Tel.: +14 04 002 9810; Fax: +14 04 002 9980; E-mail: bernd.jilma@meduniwien.ac.at

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Johanna Mielke[1], Bernd Jilma[2], Franz Koenig[3] and Byron Jones[1]

[1]Statistical Methodology, Novartis Pharma AG, 4056 Basel, Switzerland, [2]Department of Clinical Pharmacology, Medical University of Vienna, 1090 Vienna, Austria, and [3]Center for Medical Statistics, Informatics and Intelligent Systems, Medical University of Vienna, 1090 Vienna, Austria

Keywords biosimilar drug development programmes, biosimilarity, biosimilars, EMA, EPAR, trial design

British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2018) 84 1415–1431 1415

SYSTEMATIC REVIEW AND META-ANALYSIS

An update on the clinical evidence that supports biosimilar approvals in Europe

AIM
In 2006, Omnitrope (by Sandoz) was the first app
are on the market. The present study compared t

METHODS
We summarized the findings of a comprehensive
using the European public assessment reports (EP
pared were, among others, the number of patient
equivalence margins for pharmacokinetic (PK)/ph

RESULTS
The variability between the clinical development
product; if, for example, the PD marker can be as
However, even for products with the same referen
same.

CONCLUSIONS
There seems to be flexibility for sponsors regardir

Correspondence Bernd Jilma, Department of Clinical Pharmacology, Medical University of Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria. Tel.: +43 1 40400 2981; Fax: +43 1 40400 2998; E-mail: bernd.jilma@meduniwien.ac.at

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Johanna Mielke[1], Bernd Jilma[2], Byron Jones[1] and Franz Koenig[3]

[1]Statistical Methodology, Novartis Pharma AG, 4056 Basel, Switzerland, [2]Department of Clinical Pharmacology, Medical University of Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria, and [3]Center for Medical Statistics, Informatics and Intelligent Systems, Medical University of Vienna, Spitalgasse 23, 1090 Vienna, Austria

Keywords clinical trials, drug development, statistics and study design, systematic review

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Sample Size for Multiple Hypothesis Testing in Biosimilar Development

Johanna Mielke[a], Byron Jones[a], Bernd Jilma[b], and Franz König[b]

[a]Novartis Pharma AG, Basel, Switzerland; [b]Medical University of Vienna, Vienna, Austria

ABSTRACT
In biosimilar development, often multiple endpoints within a study, multiple doses and routes of administration or multiple studies in different populations are considered. However, a regulatory requirement is that equivalence of the biosimilar and the reference drug has to be shown for all comparisons, which would typically require a large sample size for a clinical development program. One way that the sample size can be reduced, when m null hypotheses are to be considered, is to require that only $k < m$ null hypotheses have to be rejected to get approval. In fact, this is a realistic requirement, since despite their guidelines the European Medicines Agency (EMA) has already approved applications for biosimilars where not all primary endpoints met the equivalence criteria. In this article, we investigate the properties of the test for the success of at least k out of m endpoints and discuss several multiplicity adjustments that might be useful in practice. We illustrate the impact of
of pharmacokinetic studies
materials for this article are

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KEYWORDS
Biosimilars; Equivalence testing; Multiple endpoints; Multiple testing; Sample size estimation

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https://doi.org/10.1080/19466315.2020.1730233

Taylor & Francis Group

Testing Procedures for Claiming Success on At Least *k* Out of *m* Hypotheses With an Application to Biosimilar Development

Johanna Mielke[a], Byron Jones[a], Martin Posch[b], and Franz König[b]

[a]Novartis Pharma AG, Basel, Switzerland; [b]Medical University of Vienna, Vienna, Austria

1. Introduction

A biosimilar, or follow-on bi
is highly similar to the refere
differences in clinically inact
produced as a cheaper copy
biosimilars is predicted to l
costs of biologics in the Un
(Miller 2013). Since several p
already expired and many r
(Generics and Biosimilars In
biosimilars has recently bec
ceutical industry.

If this development is to
cost and time needed to get a
sample sizes to the minimum
important. In this article, we
be very useful when trying
is motivated by the results o
development programs for b

ABSTRACT
Multiplicity is a common issue in clinical drug development and there exists many proposals for the handling of multiple testing in clinical trials. However, the literature on testing procedures for claiming success on at least k out of m tests and the operating characteristics of these procedures is still sparse. Such testing is very relevant in biosimilar drug development, for example, where products have gained regulatory approval in the past, even though not all hypotheses could be rejected. Obviously, simple adjustments for multiplicity like the Bonferroni-adjustment or the Holm-procedure are valid as well for this testing problem, but can be conservative. In this article, we propose simple testing procedures for claiming success on at least k out of m tests which are more powerful than standard procedures while still providing strong control of the family-wise error rate. We illustrate their applicability in practice using an example from biosimilar drug development. In the supplementary materials, we provide proofs of the properties of our

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KEYWORDS
Biosimilarity; Closed testing; Equivalence testing; Multiple testing; Multiplicity

H2020 IMI funded project

EU-PEARL
EU PATIENT-CENTRIC CLINICAL TRIAL PLATFORMS

https://eu-pearl.eu/

- IMI call to establish standards for collaborative integrated platform trials
- Involves regulatory authorithy (PEI) as beneficary
- EMA representative (Dr Andrew Thomson) in advisory board
- 2 EU-PEARL stakeholder workshops
- Foresee different ways of regulatory interactions
  - EMA ITF meeting, CTFG, FDA, …
- Organisation of scientific sessions with EMA participation
- Statistical topics of regulatory relevance include multiplicity, adaptivity, use of non-concurrent control data, clinical trial simulations (Meyer et al, Zehetmayer et al, Bolfill et al.)
- Joint publication with regulatory statisticians

The IMI has a recommondation of the scientific committee on how to engage with regulators

imi innovative medicines initiative

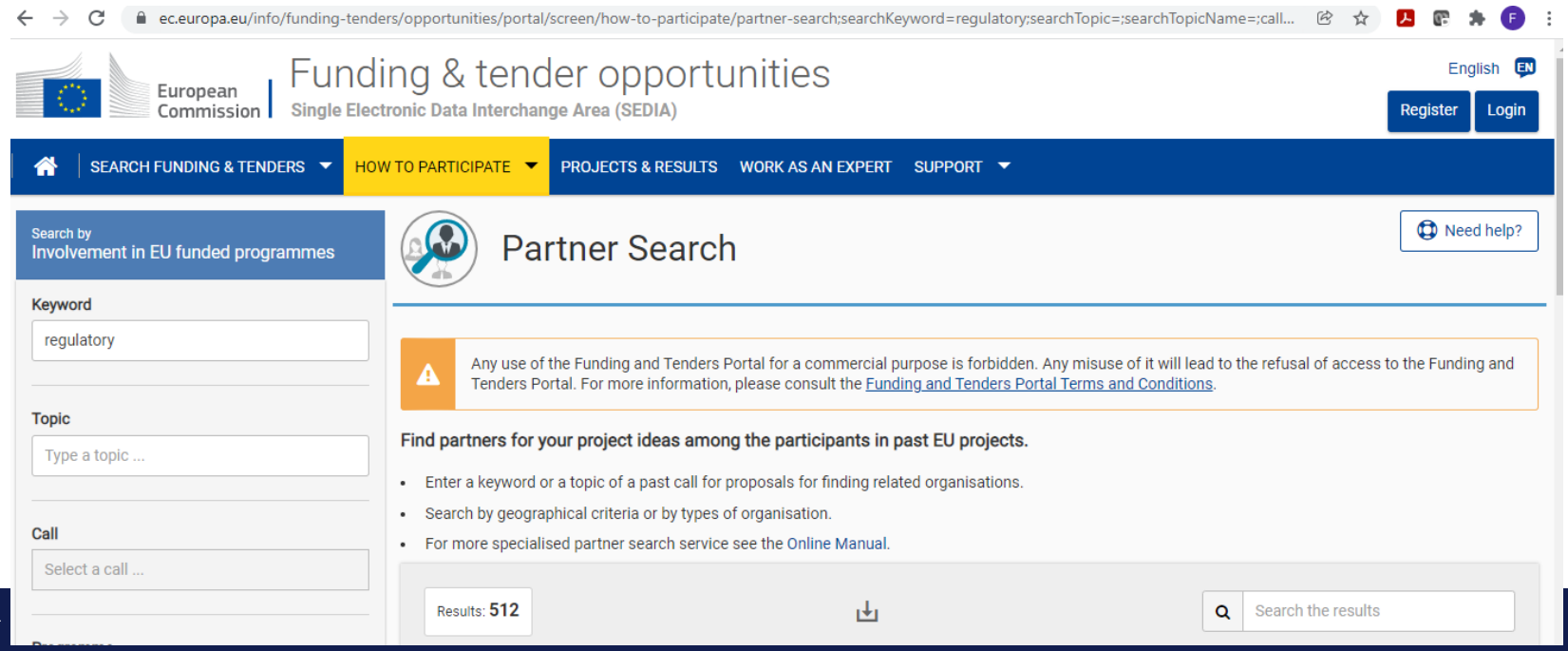
EU-PEARL has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 853966-2

How to involve regulators in project proposals

- Include regulators as
  - Full or associated partner, host for secondments, member of advisory boards, reviewers, regulatory advices (SA, PA, ITN meetings, …)
- Foresee sufficient budget for
  - Research visits (especially valuable for early stage researchers)
  - Scientific advices
  - Joint workshops, seminars etc
  - Open access for joint publications

How to find potential partners?

- Networking via conferences, societies
- Contact directly potential collaborators
- Look for potential partners interested in the same topic at webpage provided by EU commission



Controversial discussion is needed to bring regulatory science forward

PERSPECTIVES

OPINION

The risks of risk aversion in drug regulation

Hans-Georg Eichler, Brigitte Bloechl-Daum, Daniel Brasseur, Alasdair Breckenridge, Hubert Leufkens, June Raine, Tomas Salmonson, Christian K. Schneider and Guido Rasi

Abstract | Drugs are approved by regulatory agencies on the basis of their assessment of whether the available evidence indicates that the benefits of the drug outweigh its risks. In recent years, regulatory agencies have been criticized both for being overly tolerant of risks or being excessively risk-averse, which reflects the challenge in determining an appropriate balance between benefit and risk with the limited data that is typically available before drug approval. The negative consequences of regulatory tolerance in allowing drugs onto the market that turn out to be unsafe are obvious, but the potential for adverse effects on public health owing to the absence of new drugs because of regulatory risk-aversion is less apparent. Here, we discuss the consequences of regulatory risk-aversion for public health and suggest what might be done to best align acceptance of risk and uncertainty by regulators with the interests of public health.

Regulatory agencies are tasked to ensure that only those drugs for which the benefits outweigh the risks are licensed. However, there are no hard and fast rules, and different stakeholders may arrive at divergent conclusions when balancing the expected benefits of a drug against the harms it might cause once allowed onto the market. In addition, pre-licensing studies can only provide estimates of benefits and risks, which leaves room for uncertainty around the size of the effect and the probability of harm in a given patient population ('known unknowns'). There is also a chance — usually not quantifiable — that hitherto unsuspected adverse effects might become apparent only after licensing ('unknown unknowns').

Against this background, two questions become paramount: first, how much risk is acceptable for a given or anticipated benefit? Second, how much uncertainty is acceptable at the time of marketing authorization? Over the past decade, regulators have often been criticized for being overly risk-tolerant and accepting too much uncertainty when approving drugs but, at the same time, they have also been criticized for being overly risk-averse and requesting too much data or delaying decisions because of an unwillingness to leave room for uncertainty.

In this article, we share our reflections about these two key questions, examine the consequences of risk aversion for public health, and speculate what might be done to best align regulators' risk acceptance with the interests of public health. Individual regulators and other stakeholders have disparate notions of 'risk'; these include the concepts of uncertainty, hazards and the probability of adverse events[1]. For the purpose of this discussion, we initially take a broad perspective of the term 'risk', including all of the above concepts.

Errors and consequences

Every decision provides an opportunity for error and unintended consequences — drug licensing decisions being no exception. Adapting concepts previously proposed by Beckman *et al.*[2] and Manski[3], we define the following distinct errors and unintended consequences in regulatory decision-making.

- A type I regulatory error: this describes a false-positive decision to license a drug, to allow it to stay on the market or to allow it on the market for a defined subset of patients, if or where it causes more harm than good.
- A type II regulatory error: this describes a false-negative decision to deny a drug a licence, to withdraw it from the market or to restrict its use in a subset of patients, if or where it would have caused more good than harm. It is important to note that a type II error that resulted in a delay of a few months is different in terms of consequences for public health from one that permanently kept a drug off the market.
- The opportunity cost associated with the unwillingness to accept some uncertainty: all research and development (R&D) resources are finite. Hence, the request from a regulatory agency for more data to reduce uncertainty about one product will not only delay the potential public health benefit from that medicine, but will also have the indirect and unintended consequence that the resources required are no longer available for R&D into another medicine that might yield more public health gain (Beckman *et al.*[2] refer to the opportunity cost as a 'type III error', but we do not use this terminology in the context of drug regulation because, unlike type I and type II errors, it is not binary and of a very different nature).

Type I regulatory errors have been discussed extensively in the medical and mainstream press; here, we focus on type II regulatory errors and opportunity costs.

"First, do no harm" or public health?

"First, do no harm" is one of the principal precepts of medical ethics that health care professionals — including many regulators — have been taught. The origin of the phrase is uncertain but is often ascribed to Hippocrates; his eponymous oath includes the promise "to abstain from doing harm". In modern language, the approach may be considered to describe a rigid interpretation

COMMENT

The risks of methodology aversion in drug regulation

Peter Bauer and Franz König

Decisions made by drug regulatory agencies require a high level of expertise in statistical methodologies. Without urgent efforts to enhance the level of such expertise in European regulatory agencies, there is a risk that they will not be able to meet emerging challenges such as quantitative modelling of benefit–risk profiles, wider use of innovative trial designs and greater public transparency of clinical trial data.

A recent paper in this journal by senior figures from the European regulatory environment discussed the risks of risk aversion in drug regulation[1]. The authors highlight that good drug regulation is not just about minimizing the risks from false-positive decisions to license a drug or to allow it to stay on the market when it actually does more harm than good; rather, it is also about giving due consideration to the potential for adverse effects on public health owing to the absence of new drugs because of regulatory risk aversion — that is, false-negative decisions to deny a drug a license or to withdraw it when it actually does more good than harm. Beyond a certain 'sweet spot', increased regulatory risk aversion will result in diminishing public health gains from drug discovery and development, in part owing to the opportunity costs associated with gathering further data to reduce uncertainty about risks.

The authors also discuss how the risks of risk aversion can be averted in a general climate in which regulators may be more likely to be criticized for being overly tolerant of risks than for being excessively risk-averse[1]. In their opinion, a key aspect in the potential way forward is to find ways of more effectively incorporating the willingness of patients to accept risk into regulatory decision-making, and the authors highlight recent projects coordinated by the European Medicines Agency (EMA) that have identified a number of (quantitative) methods that could lend themselves to support benefit–risk decisions on drugs[1] (see the EMA report titled "Benefit-risk methodology project" and the PROTECT Consortium's report titled "Review of methodologies for benefit and risk assessment of medication" for further information). They state that the "adoption of such methodology, once properly validated in this setting, will not only serve to better explain licensing decisions to external stakeholders but also enable regulators to move away from 'first do no harm' by incorporating, in a fully transparent way, patients' values into the decision-making process"[1].

From our own regulatory experience at the EMA (F.K.) and in the Paediatric Committee of the EMA (P.B.), such as initiating the concept paper on extrapolation from adult to paediatric populations (see the EMA draft titled "Concept paper on extrapolation of efficacy and safety in medicine development" for further information), it will be challenging to find broad agreement from all stakeholders on a quantitative model for balancing the benefits and risks of a new drug that accounts for the various types of gains, costs and uncertainties. Nevertheless, we fully support the general idea (although we are cautious about what can be achieved in practice), and we consider it laudable that influential and experienced persons from the regulatory environment have made such suggestions about how regulatory decisions may be supported by statistical methods from existing toolboxes.

However, without in-depth knowledge, even existing toolboxes may quickly turn into black boxes. Furthermore, leading decision-makers in the European regulatory environment may not be going through sophisticated methodological details themselves when pioneering innovative approaches to drug regulation or ultimately applying them routinely. So, a key question is: who will they be supported by in actually doing such analyses, and who will cope with the potentially increasing workload in the future if such approaches become more popular?

This is of particular concern because a fairly recent survey indicated that less than half of the national competent authorities in European countries have educated statisticians in their staff[2]. We find it remarkable that the current workload with regard to statistical methodology for assessment procedures can be managed under these conditions. Furthermore, there is a rapidly growing need for additional specific expertise in methodology related to areas such as innovative trial designs, modelling and simulation[3], and also as a consequence of the drive for transparency in clinical trial data at the individual

Peter Bauer and Franz König are at the Center for Medical Statistics, Informatics, and Intelligent Systems, Section for Medical Statistics, Medical University of Vienna, Spitalgasse 23, 1090 Vienna, Austria.
e-mails: peter.bauer@meduniwien.ac.at; franz.koenig@meduniwien.ac.at
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Future expectations?

- Inclusion of EMA into project proposal with regulatory relevance as FULL beneficary
- Advanced educational programs to enhance regulatory science
- Take the new EMA list as starting point for future applications

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MAIN PAPER

WILEY

A proposal for a new PhD level curriculum on quantitative methods for drug development

T. Jaki[1] | A. Gordon[1] | P. Forster[1] | L. Bijnens[2] | B. Bornkamp[3] | W. Brannath[4] | R. Fontana[5] | M. Gasparini[5] | L.V. Hampson[3] | T. Jacobs[2] | B. Jones[3] | X. Paoletti[6] | M. Posch[7] | A. Titman[1] | R. Vonk[8] | F. Koenig[7]

[1] Lancaster University, Department of Mathematics and Statistics, Lancaster, UK
[2] Janssen Pharmaceutica NV, Beerse, Belgium
[3] Novartis Pharma AG, Basel, Switzerland
[4] University of Bremen, KKSB and IfS Faculty 3 – Mathematics/Computer Science, Bremen, Germany
[5] Politecnico di Torino, Turin, Italy
[6] INSERM CESP-OncoStat Institut Gustave Roussy & Université Paris-Saclay UVSQ & Service de Biostatistique et d'Epidémiologie, Gustave Roussy, Villejuif, France
[7] Medical University of Vienna, Center for Medical Statistics, Informatics, and Intelligent Systems, Vienna, Austria
[8] Bayer AG, Berlin, Germany

Correspondence
F. Koenig, Center for Medical Statistics, Informatics, and Intelligent Systems, Medical University of Vienna, Vienna, Austria.
Email: franz.koenig@meduniwien.ac.at

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This paper provides an overview of "Improving Design, Evaluation and Analysis of early drug development Studies" (IDEAS), a European Commission–funded network bringing together leading academic institutions and small- to large-sized pharmaceutical companies to train a cohort of graduate-level medical statisticians. The network is composed of a diverse mix of public and private sector partners spread across Europe, which will host 14 early-stage researchers for 36 months. IDEAS training activities are composed of a well-rounded mixture of specialist methodological components and generic transferable skills. Particular attention is paid to fostering collaborations between researchers and supervisors, which span academia and the private sector. Within this paper, we review existing medical statistics programmes (MSc and PhD) and highlight the training they provide on skills relevant to drug development. Motivated by this review and our experiences with the IDEAS project, we propose a concept for a joint, harmonised European PhD programme to train statisticians in quantitative methods for drug development.

KEYWORDS
development of early-stage researchers, drug development, PhD curriculum, regulatory statistics, university-industry partnership

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