InSPiRe
Innovative Methodology for Small Populations Research
FP HEALTH 2013 – 602144

Summary of Work Plans

This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement number FP HEALTH 2013 – 602144.

Contents

Abstract

HEALTH.2013.4.2-3 identifies a need for new or improved statistical methodology for clinical trials for the efficient assessment of safety and/or efficacy of treatment for small population groups. The InSPiRe project team brings together a team of international experts in innovative clinical trial design methodology in these specific areas along with key stakeholders including regulatory authorities, clinicians, industry and representatives of patient groups.

We will focus on four specific areas where we believe there are particular challenges. These are:

1. Early phase dose-finding studies in small populations
2. Decision-theoretic methods for clinical trials in small populations
3. Confirmatory trials in small populations and personalised medicines
4. Use of evidence synthesis in the planning and interpretation of clinical trials in small populations and rare diseases.

We will build on recent research advances, of our own and of others in this area. In the rare disease setting, we will focus on Bayesian and decision-theoretic methods that formally enable comparison of the gain in information with the cost, both in economic and opportunity terms, of clinical experimentation, and assess how information from outside the trial can formally be incorporated into the design and decision-making processes. In the personalised medicine setting, we will develop methods that allow evaluation of efficacy in a number of sub-populations simultaneously in a confirmatory clinical trial without any reduction in scientific or statistical rigour.

Concept

HEALTH.2013.4.2-3 identifies a need for new or improved statistical methodology for clinical trials for the efficient assessment of safety and/or efficacy of treatment for small population groups.

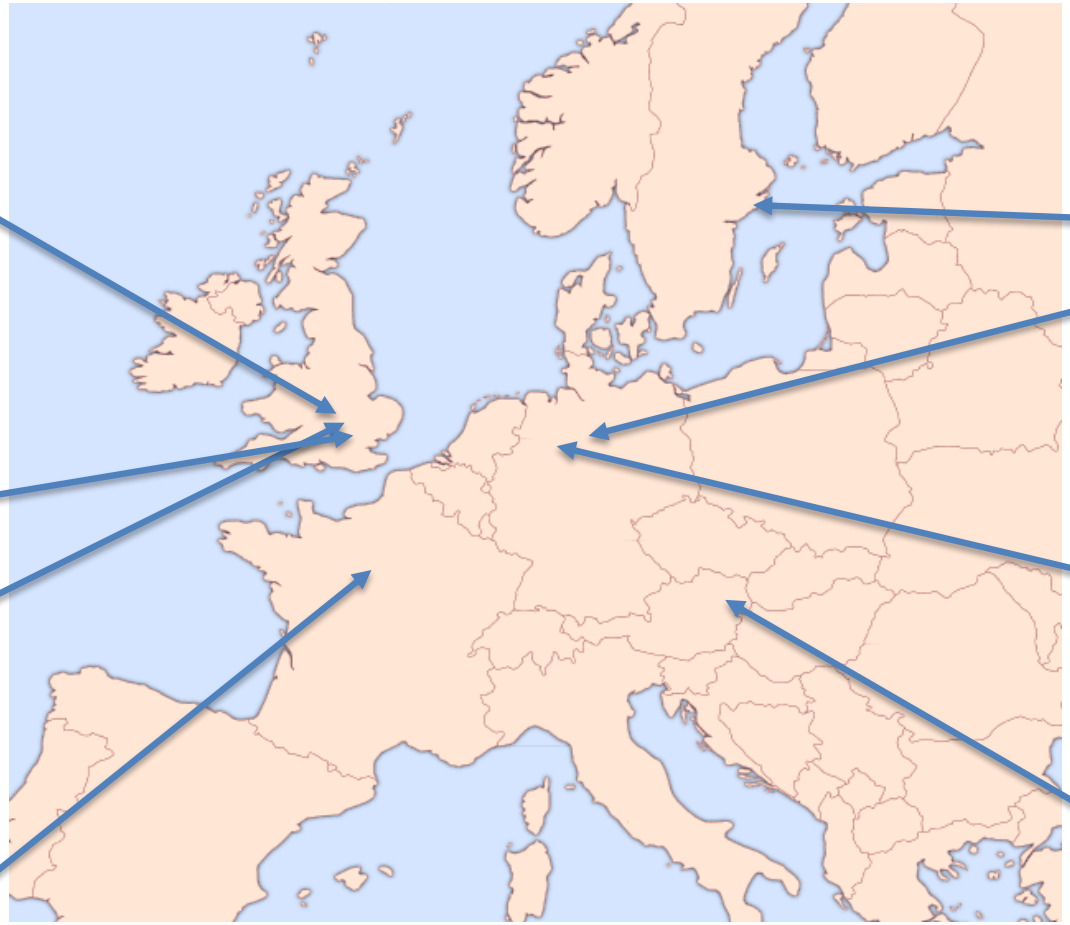
Clinical trials in small populations present a number of novel statistical challenges associated with the need to draw inference from the necessarily small sample sizes. The EMEA CHMP Guideline on Clinical Trials in Small Populations (CHMP, 2007) and the report of the US Institute of Medicine Committee on Strategies for Small-Number-Participant Clinical Research Trials (Evans and Ildstad, 2001) propose a number of potential statistical approaches. These include efficient trial designs, such as sequential and adaptive methods, and innovative methods that enable data from outside the trial to be used both at the design stage and assimilated with trial data in the final inferential process. Based on the recommendations of these guidelines and building on recent relevant methodological advances in this area, the aim of this project is to develop novel statistical methodology for clinical trials in small populations.

We have identified four specific areas where we believe novel methodology for clinical trial design is needed and achievable. These are (i) early phase dose-finding studies in small populations, (ii) decision-theoretic methods for clinical trials in small populations, (iii) confirmatory trials in small populations and personalised medicines, (iv) use of evidence synthesis in the planning and interpretation of clinical trials in small populations and rare diseases. These four areas will form the four main Work Packages, WP1, WP2, WP3 and WP4, of the project

The project team brings together a team of international experts in innovative clinical trial design methodology along with key stakeholders including regulatory authorities, clinicians, industry and representatives of patient groups. Team members have been carefully chosen for their knowledge and experience in the four key areas listed above. Strong working relationships already exist between many members of the team, with a track record of published work and grant funding as evidence of successful previous collaborations. This makes us confident that we can work effectively on this project to meet the objectives described below and to address the need stated in HEALTH.2013.4.2-3.

Project Partners and Personnel

The InSPiRe project is led by the University of Warwick, in collaboration with 7 other partners from Austria, France, Germany, Sweden and the UK.



Partner 1:
University of Warwick (UoW), UK

Partner 6:
Stockholm University, Sweden

Partner 2:
Universitaetsmedizin Goettingen, Georg-August-Universitaet (UMG-GOE), Germany

Partner 7:
Quintiles Ltd, UK

Partner 5:
Federal Institute for Drugs and Medical Devices (BfArM), Germany

Partner 8:
Clinical Trials Consulting and Training Ltd (CTCT Ltd), UK

Partner 3:
Medizinische Universitaet Wien (MUW), Austria

Partner 4:
French National Institute of Health and Medical Research (INSERM), France

Partner 1: University of Warwick, UK (Coordinating Institution)

The University of Warwick is a research-led University of international standing, ranked seventh overall in the UK-wide Research Assessment Exercise (RAE) in 2008. It prides itself on its distinctive track record for pioneering and fostering high-quality interdisciplinary research.

Warwick Medical School (WMS) was established in 2000 and since then has rapidly built a reputation for research excellence, being ranked tenth in the UK RAE 2008 for Health Services Research and has an annual grant income of £20m per year including FP7 grant funding.

Methodological expertise within WMS is primarily to be found in the Statistics and Epidemiology group, led by Professor Stallard, and Warwick Clinical Trials Unit (WCTU). The groups have particular interest in innovative methods for clinical trial design and analysis and have received funding for methodological research from UK Medical Research Council and UK National Institute of Health Research and charities including the UK Multiple Sclerosis Society.

Nigel Stallard (Project Coordinator and WP2 lead)

Nigel Stallard is Professor of Medical Statistics and leads the Statistics and Epidemiology group at Warwick Medical School. He is an expert on innovative statistical methodology for clinical trials, and has over 50 peer-reviewed publications in this area. He has particular expertise in adaptive clinical trial design and decision-theoretic methods for small and early phase clinical trials.

Susan Peach (Project Manager)

Susan Peach is the Project Manager for InSPiRe at Warwick Medical School. Sue will provide effective operational and financial management as well as administrative support for the project to ensure it is delivered to agreed timescales and budget.

Jason Madan (Deputy WP2 lead)

Jason Madan is Assistant Professor in Health Economics in WCTU. He is an expert of health economic evaluation and value-of-information methods.

Siew Wan Hee

Siew Wan Hee is a Research Fellow in Warwick Medical School. She has recently completed a PhD on decision-theoretic clinical trial methods supervised by Stallard and has expertise in clinical trial design and conduct, particularly in oncology. Hee is an expert on innovative statistical methodology for clinical trials, particularly adaptive clinical trial design and decision-theoretic methods, and has a track record of published work in decision-theoretic methods for small and early phase clinical trials.

Partner 2: Universitaetsmedizin Goettingen, Georg-August-Universitaet (UMG-GOE), DE

Founded in 1737, the Georg-August University Goettingen is a research-led University of international standing ranked second nationally and 70th globally in the most recent Times Higher Education (THE) World University Rankings. The University is part of the Goettingen Research Campus (GCR) which includes a number of federal research institutes such as the German Primate Centre and several Max-Planck Institutes.

The University Medical Centre (UMG-GOE), an established Centre of Excellence in Neuroscience and Cardiovascular research in Europe, benefits from steadily expanding collaborative research networks within the GCR. The Department of Medical Statistics is one of four Departments in the Centre for Informatics, Statistics and Epidemiology (CISE) with more than 20 research staff. The activities of the Department include clinical cooperation's, a biostatistical advisory service, research in statistical methodology and teaching. The statistical research within the Department focusses on innovative designs for clinical trials, methods for systematic reviews and meta-analyses as well as data analysis strategies for high-dimensional data and nonparametric statistics. This research is fostered through collaborations within the Centre for Statistics which provides a platform for joint research and research training across the various faculties and departments.

The Department of Medical statistics currently receives research funding from the European Commission, the BMBF (German Ministry for Education and Research), and the DFG (German Research Council).

Tim Friede (WP4 lead)

Tim Friede is Professor of Biostatistics, Director of the Centre for Statistics, Informatics and Epidemiology, Chair of the Department of Medical Statistics and co-founder of the Systematic Review Unit at the University Medical Centre Goettingen. He has worked in industry and academia in several countries including the UK, Switzerland and Germany. He has expertise in clinical biostatistics including clinical trial design and systematic reviews/meta-analysis and has collaborated with other work package leaders including Stallard and Posch leading to publications and successful grant applications. He is collaborating with the German Centre for Multiple Sclerosis (MS) in Childhood and Adolescence, has supported analyses of the European Alport Registry and is statistician of the EARLY PRO-TECT trial in children with Alport disease. He is principal investigator in the DZHK (German Centre for Cardiovascular Research) and in the European Register for Multiple Sclerosis (EUReMS).

Christian Röver

Christian Röver is a postdoc working with Friede at Universitaetsmedizin Goettingen, Georg-August-Universitaet (UMG-GOE**).** Röver has experience in systematic reviews and Bayesian methods.

Steffen Unkel

Steffen Unkel is a Research Fellow in the Department of Medical Statistics, University Medical Centre Göttingen.

Partner 3: Medizinische Universitaet Wien (MUW), AT

The Medical University of Vienna (MUW) is the largest medical organisation in Austria and one of the top-level research institutions in Europe providing Europe's largest hospital, the AKH in Vienna. The Section of Medical Statistics at the Center for Medical Statistics, Informatics and Intelligent Systems (CEMSIIS) has a strong research tradition in cooperative research projects designing and analysing clinical trials. It is a leading research center in statistical methodology for innovative clinical trial design focussing on the development of adaptive design methodology for confirmatory clinical trials and the development of multiple testing procedures for the analysis of clinical trials with multiple objectives.

Besides the methodological work, the department is involved in numerous scientific collaborations with clinical colleagues at the MUW. Furthermore, the Section of Medical Statistics is responsible for the statistics education in the curricula for human and dental medicine at the University.

Currently the department hosts 15 statisticians of which 9 hold a PhD. Weekly internal seminars as well as regular talks co-organized with the Viennese Section of the Austrian-Swiss Region of the International Biometric Society support collaborations with internal and external scientists. The department provides an excellent research infrastructure, with a comprehensive library, electronic access to all relevant journals and simulation servers which are currently upgraded. The CEMSIIS hosts also the Section of Clinical Biometrics which has an extensive expertise in Survival Analysis and Exact Tests.

Martin Posch (WP3 lead)

Martin Posch is Professor and head of the Medical Statistics Section at the Medical University of Vienna. He has extensively published on the theory of adaptive designs and multiple comparisons with focus on clinical trials and large scale testing problems in genetic research. He speaks regularly as invited speaker at international scientific conferences on Biostatistics and Drug Development. He has rich experience in planning and analysis of clinical trials. From 2011-2012 he was scientific administrator at the European Medicines Agency (EMA) and involved in the development of guidelines and assessment of study protocols. Currently he is observer of the EMA Biostatistics Working Party and Member of the Austrian Arzneimittelbeirat. He serves as Associate Editor of Biometrics and Biometrical Journal. His previous experience includes consultant on adaptive designs and multiple comparisons for the Novartis Statistical Methodology Group.

Alexandra Graf

Alexandra Graf is Assistant Professor in the Medical Statistics Section at the Medical University of Vienna. She has experience in methodological research experience and has published on the theory of adaptive designs (Graf and Bauer, 2011). Furthermore, she has extensive experience in applied statistics and cooperated in numerous clinical studies as statistical expert.

Thomas Ondra

Thomas Ondra is a PhD student and investigates methods for identification and confirmation of targeted subgroups. He obtained his Master of Science in mathematics, with specialisation in applied mathematics and scientific computing, at University of Vienna.

Partner 4: French National Institute of Health and Medical Research (INSERM), FR

Founded in 1964, the French National Institute of Health and Medical Research (INSERM) is a public scientific and technological institute under the joint authority of the French Ministry of health and French Ministry of Research. INSERM has a wide range of facilities, either directly involved in fundamental research, or in close contact with patients, thanks to cooperation with other training programs in major innovative projects.

Sarah Zohar (WP1 lead)

Sarah Zohar is a research associate at INSERM unit U872 team 22, Paris (centre des Cordeliers). Zohar has made many methodological contributions in the adaptive dose-finding area and has applied these methods in paediatric clinical trials. She has collaborated with physicians in the planning, conducting and analysing clinical trials and with international methodological experts from USA, Japan and Europe and has been invited to speak at a number of international scientific meetings.

Zohar also has considerable experience in the application of theoretical concepts in clinical trials, for instance, in early phase clinical trials, several dose-finding phase II and single arm phase IIA in paediatrics have used innovative alternative designs (Merlin 2009, Treluyer 2005, Desfrere 2005). She is co-applicant on a currently EU FP7 funded project, NEMO, a multicentre European study of neonatal seizures and their treatment uses a design developed by one of our partners (Zohar 2006).

Emmanuelle Comets (Deputy WP1 lead)

Emmanuelle Comets is a research associate at INSERM and works in the Center for Clinical Investigation (CIC 0203) located in the Hospital Pont Chaillou, Rennes. She has a PhD in biomathematics, and expertise in the development of statistical methods in nonlinear mixed-effect models and their application to clinical trial data in pharmacokinetics and pharmacodynamics (e.g. in rheumatology, cardiology, infectious diseases). She has developed R packages for model evaluation and parameter estimation in nonlinear mixed-effect models, and contributed to the PFIM software performing optimal design for these models.

Corinne Alberti

Corinne Alberti is a Professor in epidemiology at Robert Debré's hospital, Paris which is dedicated to the treatment of children. She is the director of the Clinical Investigation Centre – Clinical Epidemiology (Inserm CIE 5) and also responsible of the Unit of Clinical Research for the APHP sponsor (Assistance Publique des Hôpitaux de Paris). She is an epidemiologist active in paediatric clinical research for more than 10 years.

Moreno Ursino

Moreno Ursino is a Research Fellow in Centre de Recherche des Cordeliers de Jussieu (CRC). Ursino's main research interest is in Biostatistics, in particular in statistical genetics, in ordinal data arising from patients (VAS) pain score and dose finding. His primary role is to review literature and code and compare existing methods. He is a mathematical engineer with a PhD in Biostatistics, awarded from the Politecnico di

Torino in 2014, thesis title “Ordinal data: a new model with applications”, supervisor professor Mauro Gasparini. He worked in collaboration with doctors of the Gastroenterology Ward of Cardinal Massaia Hospital (Asti – Italy), to analyze ordinal data arising in patients using VAS pain intensity scale, and with biologists of HuGeF (Turin – Italy), on statistical genetics.

Partner 5: Federal Institute for Drugs and Medical Devices (BfArM), DE

The Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM) is an independent higher federal authority within the portfolio of the German Federal Ministry of Health. The BfArM is the successor to the Institute for Drugs (Institut für Arzneimittel) founded in 1975 as part of the now dissolved Federal Health Office (Bundesgesundheitsamt, BGA). Today, roughly 1000 employees including physicians, pharmacists, chemists, biologists, lawyers, engineers, technical assistants and administrative staff work at the BfArM with the aim of preventing health risks by continuous improvement in the safety of medicinal products and medical devices as well as monitoring legal traffic in controlled substances scheduled in the UN-Conventions of 1961, 1971 and 1988.

One of the main tasks of the BfArM is authorisation of medicinal products, reviewing the proof of efficacy, safety, and adequate pharmaceutical quality. The Biostatistics and Special Pharmacokinetics Unit is a part of the BfArM’s research department and is responsible for biostatistical and pharmacometrical assessments within the drug licensing process of European and national drug approval procedures as well as the biostatistical support of the BfArM’s research.

Norbert Benda (Deputy WP4 lead)

Norbert Benda has been head of the Biostatistics and Special Pharmacokinetics Unit at BfArM (Germany) since 2010. He has previously published joint work with Friede (Benda et al, 2010). He is member of the Biostatistics Working Party of the Committee for Medicinal Products for Human Use (CHMP) at the EMA and alternate member of the CHMP’s Scientific Advice Working Party. Before joining the BfArM he was a Senior Expert Statistical Methodologist at Novartis Pharma AG, Basel. He has 12 years of experience as a statistician in the pharmaceutical industry and 7 years as a university lecturer in Statistics. He graduated in mathematics from Aachen University and obtained a PhD from the Free University of Berlin. Benda will provide a regulatory perspective on the work package and will serve as deputy work package leader.

Frederike Lentz (née Behn)

Frederike Lentz has been a pharmacometrics specialist at the BfArM for more than three years. She is a member of the newly founded modelling and simulation working group of the Committee for Medicinal Products for Human Use (CHMP) at the European Medicines Agency (EMA). She worked as a scientific assistant at the University of Bonn for almost 4 years and a year at the Université Paris Descartes in pharmacokinetics, population pharmacokinetics, PK/PD-modeling and pharmacogenetics, mainly in the fields of oncology, diabetes and paediatric cardiology. She obtained a PhD in clinical pharmacology from the University of Hamburg in 2002. Lentz will contribute to the oversight and direction of the research of the work package, bringing expertise in pharmacometrics modelling as well as a regulatory perspective.

Partner 6: Stockholm University, SW

Stockholm University, located in Sweden's capital city, is the region's centre for higher education and research in science, the humanities, the social sciences and law, and a focus for the work of leading international researchers. Stockholm University is one of the 100 highest-ranked universities in the world, and one of the top 50 universities in Europe, according to several well established university ranking tables. Within Sweden, Stockholm University is one of the leading higher education institutes, holding the number one position for publication impact in the Leiden Ranking for 2011/2012.

Frank Miller

Frank Miller is a Senior Lecturer in the Department of Statistics at Stockholm University. Between 2003 and end of 2012, he has worked in the pharmaceutical industry at AstraZeneca and has substantial experience in the development and implementation of innovative trial designs in clinical programs. He is a recognized expert on adaptive clinical trial designs and methods for developing optimal designs in clinical studies due to a large number of peer-reviewed methodological publications and talks at international conferences. Miller will contribute to the oversight and direction of research of WP2. His role in WP2 will be to provide expert technical input on the development and implementation of innovative trial designs in a pharmaceutical industry setting, together with knowledge of decision-theoretic methods.

Partner 7: Quintiles Ltd, UK

Quintiles is one of the world's largest pharmaceutical services companies. The company was started 25 years ago and has developed extensive expertise in designing, conducting and analysing clinical trials around the world.

The Innovation unit within Quintiles provides strategic consulting services across multiple areas of pharmaceutical research, including statistical and pharmacological consulting. The Center for Statistics in Drug Development specialises in developing and implementing statistical methods for addressing challenging problems in clinical drug development such as innovative approaches to trial designs, analysis of incomplete data, subgroup identification and biomarker discovery.

Alex Dmitrienko (Deputy WP3 lead)

Alex Dmitrienko is Executive Director, Center for Statistics in Drug Development, Quintiles Innovation. He has over 15 years of clinical trial experience and has been actively involved in biostatistical research with emphasis on multiple testing procedures, subgroup analysis and adaptive designs in clinical trials. He is a recognized expert on multiple comparisons and has over 70 publications. He has authored/edited two SAS Press books (*Analysis of Clinical Trials Using SAS* and *Pharmaceutical Statistics Using SAS*) and a Chapman and Hall/CRC Press book (*Multiple Testing Problems in Pharmaceutical Statistics*). He is a Fellow of the American Statistical Association. Dmitrienko will contribute to the oversight and direction of the research undertaken in WP3. He will provide technical expertise in multiple testing and adaptive design issues. His extensive pharmaceutical industry experience in methodology and applications (Lipkovich et al, 2011, Millen et al, 2012) will also bring an industrial perspective to WP3.

Partner 8: Clinical Trials Consulting and Training Ltd, UK

Clinical Trials Consulting and Training Ltd is a clinical trials consulting company led by Dr Simon Day. Simon has over 30 years working in clinical trials in academia, the pharmaceutical industry, and as a regulator. He was formerly Head of the Statistics Unit, and Manager of a Product Lifecycle Assessment Team at the Medicines and Healthcare products Regulatory Agency (MHRA). He consults with companies throughout the world, with contracts in Europe, the US, Japan and Australasia.

Simon Day

Simon Day leads Clinical Trials Consulting and Training Ltd, a clinical trials consulting company. Day has considerable expertise in the application of statistical methods in clinical trials of rare diseases. He has spent much of the last 10 years of his career specialising in orphan products, designing trials to assess their efficacy and safety, and evaluating evidence from such studies. Whilst employed as Head of Statistics at the UK regulatory authority (MHRA), and acting as vice-Chairman of the Scientific Advice Working Party at the European Medicines Agency (EMA), he was lead author for the CHMP Guideline on Clinical Trials in Small Populations (CHMP/EWP/83561/2005, July 2006). He has given talks and courses on trial design and drug development of orphan products in Europe, North and South America and Japan. In particular he helped develop, and has been a major contributor, to a course run by the US Food and Drug Administration on the Science of Small Populations. The course has been run 4 times over 4 years and, through webcasting, has been viewed by thousands of researchers from all over the world.

Day has served as an Expert Evaluator to the European Commission for the FP7-HEALTH-2010-single-stage call in 2009, and the FP7-Health-2012-Innovation-1 call in 2011. He is also a member of the TREAT-NMD Advisory Committee for Therapeutics (part of the Network of Excellence on Translational Research in Europe – Assessment and Treatment of Neuromuscular Diseases). Day is also a member of the Executive Committee of ICORD (the International Conference on Rare Diseases and Orphan Drugs).

Day will contribute to the oversight and research direction of WP2. He will provide expertise on the implementation of innovative methods in a pharmaceutical industry setting and the conduct of clinical trials in rare diseases and for orphan drugs.

Consultant: Beat Neuenschwander

In addition to the eight partners listed above, Dr Beat Neuenschwander will also contribute to the project as a consultant. He has spent the last 20 years as a statistician, working as a consultant for the Swiss Federal Office of Public Health (1994-2001), and Novartis Pharmaceuticals (since 2001), where he currently has the role of a Biometrical Fellow in the Oncology Business Unit. Neuenschwander has strong expertise in observational and randomized trials. He has made significant contributions to evidence synthesis, meta-analysis, and Bayesian statistics. In particular, he has been a major contributor to the methodological development of phase I cancer trials, for which Novartis is known as the leading company world-wide. More recently, he has helped to develop and implement the meta-analytic-predictive approach to using historical data in clinical trials with sparse data.

Neuenschwander is well-known for promoting the integrated use of data, and has presented on this topic on numerous occasions at major conferences. He taught several courses in Bayesian Statistics, and has also given seminars at regulatory authorities (on Oncology Phase I trials and rare events meta-analysis at the FDA, and on evidence synthesis at the PMDA).

Work Package (WP) Descriptions

WP1: Research in early phase dose-finding trials in small populations

Objectives

Overall Objective

O1.1. Propose innovative designs for early phase clinical trials taking into account safety, efficacy and pharmacokinetic/pharmacodynamic (PK/PD) measures in order to better estimate the dose level to be recommended based on limited sample sizes and subgroups.

Specific Objectives

O1.1. Develop efficient model-based designs for dose-finding studies using PK/PD information with different continuous and binary outcomes.

O1.2. Evaluate the performance of the methods in terms of information gain, number of subjects, efficiency, and robustness.

Description of Work

In work package 1 we will develop novel methodology for improving dose-finding in early phase clinical trials by incorporating data on pharmacokinetics (PK), describing the time-course of drug concentrations in the body, and the pharmacodynamics (PD), describing the time-course of effects, including both the desired pharmacological effect and harmful side-effects of the treatment.

Early phase dose-finding studies are the first trials of a new medicinal product in humans and aim to obtain reliable information on an appropriate dose for use in further clinical trials. Sample sizes for such studies are typically small, and this is particularly true in a small population context. Recent work has led to efficient designs for dose-finding based on the minimum number of participants. These methods have generally relied primarily on observed safety data, however, and there is a growing awareness of the need to better incorporate pharmacokinetic/pharmacodynamic (PK/PD) information in the dose-finding process. In this project our aim will be to extend novel design methods to use PK/PD data more fully to

better estimate the best dose level for further evaluation whilst ensuring the sample size for early phase trials is kept to a minimum.

In this work package we will develop a new method for combination of PD and PK data. This will extend existing dose-finding methods such as those proposed by Piantadosi and Liu (1996), Whitehead et al (2001), Whitehead et al (2006) and Dragalin and Fedorov (2008). A particular area of development will be Bayesian meta-analytic methods building on our previous work in this area (Zohar et al, 2011).

The Team

WP1 will be led by **Sarah Zohar**, at INSERM, Paris.

Other members of the WP1 team include:

Emmanuelle Comets (Deputy WP1 lead)
Corinne Alberti
Frederike Lentz (née Behn)
Nigel Stallard (Project Coordinator and WP2 lead)
Moreno Ursino

WP2: Research in decision-theoretic designs for clinical trials in small populations

Objectives

Overall Objective

O2. Develop methods for small population clinical trials based on a decision-theoretic framework.

Specific Objectives

O2.1. Obtain optimised clinical trial designs based on utility functions that account for the benefits of treatment and the population size.

O2.2. Incorporate health economic aspects in design of trials in small populations using a value-of information approach.

O2.3. Determine appropriate levels of evidence for decision-making in small population clinical trials.

Description of Work

In WP2 we will develop decision-theoretic methods for designing trials in rare diseases.
Most clinical trials are designed with no reference to the size of the population in which the research is conducted. Whilst this may be reasonable in a large population, in rare diseases or other small populations it can lead to designs that are inappropriate. If the population under investigation is small, a large proportion of the patient group may be recruited to a clinical trial. Recruitment to one trial may thus have an impact on the conduct of other trials or even reduce significantly the size of the population receiving usual care. The value of one clinical trial must therefore be compared with that of other trials if research is to proceed efficiently (Stallard, 2003). We will develop novel methods for the design and sequential monitoring of small population clinical trials based on a formal comparison of the gain in information from a clinical trial with the cost of the trial.

Decision-theoretic methods explicitly enable evaluation of the level of evidence required from a clinical trial to best inform clinical practice. This in turn can lead to efficient and appropriate clinical trial design. In a small population setting, the small available sample size, the fact that recruitment to one clinical trial may limit recruitment to concurrent trials and the small size of the target population may mean that standard clinical trial designs, proposed in the setting of large patient populations, may be inappropriate. In this project we will explore the use of decision-theoretic and value-of-information methods for the design and sequential monitoring of clinical trials in small populations. This will lead to smaller studies that are more able to lead to appropriate decision-making.

The gain in information will reflect the size of the population for which the therapy is being developed, while consideration of costs will be in both resource use and opportunity terms, the latter being particularly important when a series of clinical trials is considered since in a small population recruitment to many trials simultaneously is likely to be impossible. Conventional sample size calculations will be replaced with calculations that explicitly allow for the opportunity cost associated with undertaking a trial of a certain size and sequential monitoring of trials might be used to be able to terminate trials rapidly when early results do not appear sufficiently promising. We will also explore the use of multi-arm trials in the small population setting. Such designs allow a number of potential novel therapies to be compared with each other and with a control simultaneously in a single trial. This can prove an efficient way to rapidly evaluate a number of treatments, particularly if early trial results can be used to drop effective treatments part-way through the trial (Bretz et al 2006, Stallard and Todd 2003). The decision-theoretic approach will be used to formally assess the potential benefits from such an approach as well as developing optimal strategies for choosing which treatments should be included or dropped from the trial.

The methodology developed will also build on the health economic value of information approach, and enable an assessment of the appropriate level of information required for clinical decision-making in the small population setting. Value-of-information methods have been explored extensively in the health economic literature, where value is defined in terms of the likelihood of adoption decisions changing in light of trial results, and is therefore linked to decision-making concerning the reimbursement of drugs. Extending this approach to rare diseases and small populations would be particularly novel and

challenging, since reimbursement decisions involve balancing cost-effectiveness against complex and subjective considerations of equity.

This work package will build on existing work on decision-theoretic approaches. Such methods have been proposed by a number of authors, for example, Sylvester and Staquet (1980), Stallard, Thall and Whitehead (1999), Stallard (2003) and Hee and Stallard (2012) focussing particularly on these problems in the small population setting where there is very little existing work. The explicit use of health-economic value-of-information techniques in this setting is particularly novel. The use of value-of-information approaches will be based on the work of Willan (see, for example, Willan and Pinto, 2005, and Willan and Eckermann, 2010).

The Team

WP2 will be led by Nigel Stallard, at Warwick, UK.

Other members of the WP2 team include:
Jason Madan (Deputy WP2 lead)
Simon Day
Frank Miller
Martin Posch (WP3 lead)
Siew Wan Hee

WP3: Research in confirmatory trials for small populations and personalised medicines

Objectives

Overall Objective

O.3. Develop frequentist and decision theoretic methods to predict patients' responses to targeted treatments based on genetic features or other biomarkers such that subgroups of patients for which the benefit risk balance of a treatment is positive can be identified and confirmed.

Specific Objectives

O.3.1. Develop frequentist methods for the identification and confirmation of subgroups where the benefit risk balance is positive.

O.3.2. Develop decision theoretic approaches for the identification and confirmation of subgroups.

O.3.3. Develop optimised adaptive enrichment designs and understanding of the potential improvement in efficiency achievable by adaptive designs compared to fixed sample designs

Description of Work

In WP 3 we will develop methods to predict patients' responses to targeted treatments based on genetic features or other biomarkers such that subgroups of patients for which the benefit risk balance of a treatment is positive can be identified and confirmed. While it has been shown that study designs and analysis methods based on multiple testing procedures and/or adaptive designs may be more efficient compared to standard approaches (Alosh and Huque 2010, Zhao et al 2010, Brannath et al. 2009) many of the proposed procedures are ad-hoc methods based on single biomarkers and a systematic approach to derive optimized enrichment designs and analysis methods is lacking. Furthermore, the literature focuses on efficacy and insufficient consideration is given to the establishment of positive benefit risk and the closely related problem of the estimation of treatment effects (on safety and efficacy) in targeted subgroups. Finally, current approaches address maximization of statistical power but do not take the prevalence of the identified subgroups into account.

We will derive optimised study designs based on one or more biomarkers, incorporating information from surrogate and safety endpoints to specify and confirm subgroups controlling frequentist error rates (FDA 2012, EMA 2011). This work will cover trials with different objectives, such as the identification of any subgroup, all subgroups or the maximal total population, where the treatment has a positive benefit risk balance (Millen et al 2012). The frequentist analysis approach will allow to assess the level of evidence such trials can provide in terms of current standards.

Besides optimizing the probability of success we will use decision theoretic approaches developed in WP2 to develop optimized methods for the identification of subgroups where the benefit-risk balance is positive. Especially, accounting for the prevalence of subgroups, as well as the estimated treatment effect and safety profile in different subgroups will allow incorporation of health economic aspects into the optimization of the identification and confirmation of subgroups. Also for the decision theoretic approach we will develop methods that allow incorporation of information from surrogate endpoints.

Furthermore, we will develop optimized adaptive enrichment clinical trial designs (Brannath et al 2009, Magnusson and Turnbull 2013), allowing for subgroup selection in an interim analysis. We develop methods that exploit information from one or more biomarkers and surrogate endpoints as well as safety outcomes for the selection of a subpopulation for the remainder of the trial. For the derivation of the subgroup selection rule we will apply frequentist and Bayesian decision theoretic methods.

In this work package we will build on existing methods that seek to simultaneously identify patient subgroups and confirm treatment efficacy in those subgroups including the methods proposed by Alosh and Huque (2010), Zhao et al (2010) and Brannath et al. (2009). A key objective will be the development of optimal design strategies for adaptive enrichment clinical trials, building on the work of Brannath et al (2009) and Magnusson and Turnbull (2013).

The Team

WP3 will be led by Martin Posch**,** at MUW, Austria
Other members of the WP3 team include:

Alex Dmitrienko (Deputy WP3 lead)
Tim Friede (WP4 lead)
Alexandra Graf
Frank Miller
Nigel Stallard (Project Coordinator and WP2 lead)
Thomas Ondra

WP4: Research in use of evidence synthesis in the planning and interpretation of clinical trials in small populations

Objectives

Overall objective

O.4. Develop evidence synthesis methods for small populations and rare diseases to support the planning, analysis and interpretation of a single randomized controlled trial.

Specific objectives

O4.1. Assess feasibility and utility of the newly developed methods in small populations

O4.2. Apply generalized evidence synthesis approaches to paediatric studies and compounds developed for potentially multiple rare indications

O4.3. Provide software tools for design and analysis to facilitate application of methods developed

Description of Work

In WP4 we will develop evidence synthesis methods for designing, analysing and interpreting randomised clinical trials in the context of additional non-randomised data.

Whereas in large populations usually two independent confirmatory trials are required to demonstrate efficacy and safety for regulatory purposes, in small populations the conduct of even a single large-scale confirmatory trial might be extremely difficult or not feasible. In this situation the synthesis of all available

data from different sources including observational data from disease registries, uncontrolled trials and randomised controlled trials, is extremely important since it facilitates extrapolation e.g. from one subgroup to another (EMA 2012). The focus of work package WP4 will be the formal integration of data from registries and uncontrolled studies for the planning and interpretation of a confirmatory randomised controlled study in small populations and rare diseases, linking in with work packages WP2 and WP3.

Hierarchical models provide a natural framework for the synthesis of data from various sources and extend traditional methods for meta-analyses of randomised controlled trials to network meta-analyses (also called indirect or multiple treatment comparison methods) and beyond. In what is sometimes referred to as generalised evidence synthesis, or cross-design synthesis, data from different types of data sources (e.g. randomized and non-randomized studies) are combined by explicitly modelling potential biases (Spiegelhalter et al 2004). For instance, in a fairly simple hierarchical model estimates of a parameter of interest from studies of the same study type might be considered exchangeable. In the statistical model this can be achieved by including a random study-type effect in addition to the usual random study effect in meta-analysis. These models can be extended to account for potential biases and also allow for different degrees of discounting of information from certain studies or study types.

When combining data from different sources the hierarchy in the model might be fairly clear. However, when combining data from subpopulations it might be less clear which subpopulations are exchangeable and which are not, meaning that the hierarchy in the model is less well defined. This additional uncertainty has to be incorporated in the model for proper inference. Flexible distributions of the random effects have been proposed to extend the models discussed above (Higgins et al 2009) and we will build on these methods and investigate alternatives when developing new methodology particularly suited to small populations and rare events considered in this project.

The hierarchical models, which can be fitted either using Bayesian or likelihood approaches, allow modelling of heterogeneity between studies and study types by including appropriate variance components as explained above. This is of particular importance in small populations because of the relatively small number of studies, small study sizes, larger heterogeneity in studied populations, and variations in study designs that are often more pronounced than in larger populations. The computational issues arising from these circumstances will also be dealt with in WP4.

The work will extend previous methods for evidence synthesis focussing particularly on problems in small populations and rare diseases where there is very little existing work. We will build on existing work on evidence synthesis, including that by Spiegelhalter et al (2004) and (Higgins et al 2009).

The Team

WP4 will be led by Tim Friede, at UMG, Germany.

Other members of the WP4 team include:

Norbert Benda (Deputy WP4 lead)

Beat Neuenschwander
Martin Posch (WP3 lead)
Christian Röver
Nigel Stallard (Project Coordinator and WP2 lead)
Steffen Unkel

WP5: Dissemination

Objectives

Overall Objective

O.5 Disseminate and present innovative methodological developments from work packages WP1, WP2, WP3 and WP4.

Specific Objectives

O5.1 Build and maintain awareness of the project in interested stakeholder groups including relevant statisticians, clinicians and decision makers in academic, pharmaceutical industry and regulatory settings.

O5.2 Organise and host a conference for dissemination and discussion of key project research results.

O5.3 Publish project results in high-quality peer-reviewed journals, with publications made available on an open access basis when possible.

Description of Work

The ultimate aim of all methodological development is the implementation of the novel methods, in this case improving the design, analysis and conduct of clinical trials in small populations. Whilst this can be achieved through the improvement of clinical trial guidelines to reflect the availability of efficient new methods, realistically this may not be achieved within the duration of this project. A key step on the path to guideline change is the peer-reviewed publication of methods and case studies in the statistical and medical literature. This disseminates the work and shows that the methods have been accepted by the scientific community. Our first objective is thus the publication of novel statistical methodology that we have developed and for the design, conduct and statistical analysis and interpretation of clinical trials in small populations. This will start with publication of methodological papers in high quality international peer-reviewed statistical journals such as *Statistics in Medicine* or *Biometrics.*

We will also disseminate the results widely through relevant conferences and a project website. Involvement of clinical and regulatory experts, pharmaceutical industry statisticians and patient representatives will ensure the relevance of our work to key stakeholders. This will enable our second objective; the development and publishing of case-studies illustrating the application of methodology developed to clinical trials in small populations, which will again be published in high quality peer-reviewed journals. This will initially be retrospective application to data from completed trials. We see this as an important step towards acceptance of the novel methodology, leading to prospective inclusion in clinical trial protocols. This will ensure that the methodology is disseminated and implemented as widely and rapidly as possible.

WP6: Research Management

Objectives

Overall Objective

O6. Create and maintain an organisational framework that facilitates the successful conduct of the project, guaranteeing that participants are fully integrated in the decision-making, management and delivery of the project and that financial resources are effectively managed.

Specific Objectives

O6.1. Ensure that all milestones are completed and all deliverables are delivered in time and that the consortium's contractual duties are fulfilled.

O6.1. Ensure effective communication between project participants and with third parties.

O6.3. Deliver effective management of financial resources.

O6.4. Comply with ethical requirements and collate documentation as required.

Description of Work

Professor Nigel Stallard from the University of Warwick will serve as project coordinator. He will continuously monitor the progress of the project and its work packages, ensuring that milestones are met and deliverables are delivered on time. As project coordinator, Professor Stallard will also be responsible for reporting to and communicating with the European Commission regarding the project, and will chair the project steering committee.

Susan Peach, the Project Manager will lead this work package and ensure that the project is carried out according to plan, particularly in regard to time, cost and quality. Sue will take oversight of and be responsible for all planning, steering and controlling activities, problem solving and the associated administrative work of the project. Sue will be the formal contact point for project partners, collaborators and external stakeholders and in respect of day-to-day administrative issues and will ensure effective communication between the participants. She will also develop the project website and ensure this is maintained and kept up to date. Sue will thus support the project coordinator and be the focal point for administration and communication within the project.

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