

InSPiRe Periodic Report: 01 February 2014 to 31 July 2015

1. Publishable summary

1.1 Context and objectives

The HEALTH.2013.4.2-3 call 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 brings together international experts in innovative clinical trial design methodology in these specific areas along with key stakeholders including regulatory authorities, industry, clinicians and patient groups to address this need. Our research incorporates four research-oriented work packages:

Work Package 1: Research in early phase dose-finding trials in small populations

Work Package 2: Research in decision-theoretic designs for clinical trials in small populations

Work Package 3: Research in confirmatory trials for small populations and personalised medicines

Work package 4: Research in use of evidence synthesis in the planning and interpretation of clinical trials in small populations

The overall and specific project objectives of the four main research work packages are as follows:

O.1 To 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.

O.1.1 To develop efficient model -based designs for dose-finding studies using PK/PD information with different continuous and binary outcomes.

O.1.2 To evaluate the performance of the methods in terms of information gain, number of subjects, efficiency, and robustness.

O.2 To develop methods for small population clinical trials based on a decision-theoretic framework.

O.2.1 To obtain optimised clinical trial designs based on utility functions that account for the benefits of treatment and the population size.

O.2.2 To incorporate health economic aspects in design of trials in small populations using a value-of-information approach.

O.2.3 To determine appropriate levels of evidence for decision-making in small population clinical trials.

O.3 To develop frequentist and decision theoretic methods to predict patients' responses to targeted



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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.

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

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

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

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

O.4.1 To assess feasibility and utility of the newly developed methods in small populations

O.4.2 To apply generalized evidence synthesis approaches to paediatric studies and compounds developed for potentially multiple rare indications

O.4.3 To provide software tools for design and analysis to facilitate application of methods developed.

In addition, we have the following dissemination-related objectives:

O.5 To disseminate and present innovative methodological developments from the project.

O.5.1 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.

O.5.2 To organise and host a conference for dissemination and discussion of key project research results.

O.5.3 To publish project results in high-quality peer-reviewed journals, with publications made available on an open access basis when possible.

1.2 Work performed since the start of the project

Progress on the four research-based work packages is detailed below. In addition, project results are disseminated via the project website, presentation at key national and international conferences and publication in high quality peer reviewed scientific journals.

WP1: Early phase dose-finding trials in small populations

We conducted a review assessing methods for dose-finding using pharmacokinetic (PK) information and extended the methods to modify them for a common clinical setting. This enabled us to evaluate and compare the approaches in a large simulation study, assessing the impact of utilising PK information. We also undertook a theoretical investigation of the benefit of using PK data.



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We are involved in the design of a clinical trial in neonates (LEVNEONAT) using a dose-finding method that we developed to consider multiple toxicities and binary pharmacodynamic data. Simulation studies investigating the method are ongoing.

WP2: Decision-theoretic designs for clinical trials in small populations

We completed a systematic review of decision-theoretic approaches to clinical trial design and monitoring, to appear in *Statistical Methods in Medical Research*. We developed a decision-theoretic model incorporating gains to patients within a trial and future patients receiving treatment depending on the results of the trial. We show that in many settings the optimal trial sample size is proportional to the square root of the population size. We also developed methods for the design of a series of trials of related treatments in a small population. Current work is exploring the trade-off between multiple decision-makers representing clinical trial sponsors and a societal viewpoint. We are also developing case-studies to illustrate the application of methods developed.

WP3: Confirmatory trials for small populations and personalised medicines

We completed a review of the literature on methods for identification and confirmation of targeted subgroups in clinical trials to appear in *Journal of Biopharmaceutical Statistics*.

We explored methods for identification and confirmation of subgroups in an RCT, assessing and optimizing the methods in a decision theoretic framework (Graf et al, *Biometrical Journal*, 2015). The designs are assessed based on a simple utility function that assigns quantitative utilities to possible outcomes reflecting the expected profit to the sponsor and benefit to society of an effective drug licenced for a certain population. We are currently working with the FP7 project IDeAL and the DIA Working group on Small Populations to extend the model. We will derive optimized designs and generalize the procedure to the optimization of both sample size and multiple testing procedure used. Work is also ongoing on targeted subgroups defined by a continuous biomarker.

WP4: Use of evidence synthesis in the planning and interpretation of clinical trials in small populations and rare diseases

We systematically reviewed evaluations of therapies in two rare conditions. In addition to facilitating the understanding of these conditions the review offers an overview of current practice in rare disease research.

Within the framework of a single RCT comparing experimental and control treatments in a small population, we are investigating methods that combine data from a randomized comparison and other sources to give a combined estimate of treatment effect. We have built a statistical model that mimics the design of an ongoing paediatric trial in Alport disease. We are investigating methods



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for evidence synthesis in a few small trials where meta-analyses methods face particular problems. Motivated by a recent review in immunosuppression following liver transplantation in children, we investigated commonly used frequentist and Bayesian procedures to estimate the between-trial heterogeneity in extensive simulation studies. We are developing statistical software to implement our methods.

1.3 The expected final results and their potential impact and use

Evidence-based decision-making is an essential part of modern healthcare development. This is underpinned by the randomised clinical trial (RCT), which leads to evidence on the safety and effectiveness of novel treatments. Conducting RCTs in small populations is challenging. In this setting it is thus essential that all available information is used and that the small population setting is acknowledged. Population heterogeneity can mean that RCTs need to both identify and assess treatment efficacy in population subgroups, again requiring appropriate statistical methods. The purpose of the InSPiRe project is to develop innovative methodology to address these challenges in four research-centred work packages. Novel methods developed will have a substantial impact in leading to methods that enable RCTs to be conducted more efficiently with no loss in scientific or statistical integrity or to improved inference from RCTs.

WP1 will develop innovative designs for early phase RCTs that incorporate pharmacokinetics (PK) data, describe pharmacodynamics (PD) and model both the desired pharmacological effect and harmful side-effects of the treatment. These designs will enable better estimation of the dose level to be recommended when the sample size is small or the population is comprised of a number of subgroups. Focussing on the example of paediatrics, where issues such as patient heterogeneity in age or maturation, the definition of outcome, and the identification of acceptable doses need to be addressed, we will combine medical and statistical aspects of the dose-finding problem to better estimate the dose level to be recommended for further investigation allowing for small population characteristics and prior knowledge of the drug together with innovative use of PK/PD and other external data.

WP2 will develop decision-theoretic designs for RCTs in small populations. Using Bayesian optimisation methods, these designs will lead to acceleration of RCTs in small population groups. Most RCTs are designed with no reference to the size of the population. In small populations this can lead to inappropriate designs. We will develop novel methods for the design of small population RCTs based on a formal comparison of the gain in information with the cost of the RCT. The use of sequential monitoring or multi-arm trials to improve efficiency will also be explored.

WP3 will develop methods to predict patients' responses to targeted treatments based on genetic features or other biomarkers to identify and confirm treatment effects in subgroups of patients for which the benefit risk balance of a treatment is positive. We will derive optimised study designs



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based on one or more biomarkers, incorporating information from surrogate and safety endpoints and controlling frequentist error rates. This will allow us to assess the level of evidence such trials can provide in terms of current standards. We will also develop optimized adaptive enrichment clinical trial designs, allowing subgroup selection in an interim analysis. Our methods will exploit information from one or more biomarkers and surrogate endpoints as well as safety outcomes using frequentist and Bayesian decision theoretic approaches.

WP4 will develop evidence synthesis methods for designing, analysing and interpreting RCTs in the context of other data. In small populations the conduct of even one large-scale confirmatory trial may be infeasible. The synthesis of data from all available sources including disease registries and uncontrolled trials is thus extremely important. Hierarchical models provide a natural framework for this and extend traditional methods for meta-analyses of RCTs to allow modelling of heterogeneity between studies and study types. This is particularly important in small populations with small number of studies, small study sizes, larger heterogeneity in studied populations and variations in study designs.



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