Impact Objectives

- Continue to innovate design and statistical analysis of clinical trials so as to create a more patient-focused approach
- Through a methodical approach to small trial clinical design, enable new treatments for rare diseases to reach patients faster, but also ensure the treatments are more reliable despite the obstacles created by small populations
- Ensure the 30 million people in Europe suffering from a rare disease receive the same quality of treatment as anyone else

An innovative approach to rare diseases

__Professor Kit Roes__ of the __Asterix__ project discusses his work on the design and analysis of clinical trials, introduces the innovative approaches his team are employing and explains how Asterix is bridging the gap between clinical trials and real-world evidence

Could you begin by describing the background behind Advances in Small Trials dEsign for Regulatory Innovation and eXcellence (Asterix)?

At the time of the European Seventh Framework (FP7) call for research proposals, there was already collaboration between the current partners on statistical methods for clinical trials. Given our backgrounds (Professor Dr Armin Koch, Medical School of Hannover, Germany, from the regulatory and medical school perspective, and myself with a pharmaceutical industry and medical centre background), Professor Koch and myself were logically focused on advancing drug development and regulatory decision-making, with a shared vision of improving treatment and access to treatments for patients. In both our clinical environments we are particularly involved in clinical research involving patients with rare conditions. Joining forces to focus on small populations and rare diseases was a logical step.

What are the unique features of the Asterix project?

The Asterix project has a strong basis in advancement of statistical methodology combined with regulatory and epidemiological expertise. The project steps out of the comfort zone of statisticians, getting to the patient perspective and disseminating results outside the traditional statistical research community. Additionally, we focus on what matters to patients, developing patient-centred outcomes. We also take the specifics of diseases into account in order to provide tailored clinical design and regulatory guidance. We also practise what we preach and actually apply the methods we have developed.

Could you explain the key issues facing research into rare diseases, specifically in terms of clinical trials?

The unmet need for patients suffering from a rare disease is well recognised, and regulatory systems across the globe have issued incentives to promote development of new drugs for these diseases. The incentives appear to be successful, with many more drugs being granted orphan designation. Clinical research, however, still faces substantial challenges, which Asterix aims to address. The first obvious challenge is the inherent small number of patients that can be recruited into clinical trials. Secondly, there is often substantial heterogeneity between patients suffering from the same rare diseases. Third, exploration of the challenges in clinical research for rare diseases has triggered a re-think in terms of whether the usual standards of evidence (number of trials, control of false positives, type 1 error rates, the role of meta-analysis) are adequate.

What research gaps do you see the integrated approach of Asterix filling?

Asterix's integrated approach acknowledges that to be successful, we need to push state-of-the art statistical methodology and at the same time make sure everything is moving in the right direction for patients. This impacts the regulatory environment and the need to make it practical for clinical researchers to implement. So it is not only a matter of filling research gaps, it is also about changing the way we do research.

How do you see your research developing in the future?

A strong research network is established and substantial progress has been made – but we have a shared drive that we are not finished yet. Even within the current individual topics, further room for improvement exists. In addition, I see a few high level areas that require dedicated and prolonged attention – the research has brought up fundamental questions on levels of evidence, inference and the role of randomised clinical trials versus other forms of clinical data generation. I think we need to accelerate the cycle of developing new methodology and gaining true practical experience from implementation. More work also needs to be done in the area of designing and executing clinical trials and development programmes in which multiple pharmaceutical companies and academia collaborate to advance treatments for patients with rare diseases.

Picture by CDC/Dr. Brinkman

The patient perspective

***The University Medical Center Utrecht** in the Netherlands, is coordinating an ambitious project which aims to improve the lives of those living with rare diseases by enhancing the statistical power of clinical trial design in small populations*

The combined clinical and socioeconomic impact of rare diseases is huge, with up to 8000 rare diseases affecting more than 30 million people in Europe, many of them children. Even though drug designations have been granted, few orphan drugs have reached the market. For example, in 2011 the Committee for Orphan Medicinal Products and the European Medicines found that since 2000, more than 850 orphan drug designations were granted by the European Commission, but less than 100 orphan drugs reached the market. Thus, there remains a substantial unmet need. The drugs in development need trials to be performed and for their results to be assessed by regulatory authorities. This can benefit from the methodological advances currently being pursued.

Dr Kit Roes is at the helm of the Advances in Small Trials dEsign for Regulatory Innovation and eXcellence (Asterix) project, which is working tirelessly to ensure patients suffering from rare diseases have access to the same quality of treatment as other patients. 'Although more than 1500 new therapies are designated as orphan, just over a 100 drug treatments are approved,' Roes explains.

'This means a huge number of clinical trials are needed, in a setting where it is difficult to design, conduct and interpret them due to the small populations available.'

IMPROVING LIVES

The goal of Asterix is to deliver validated innovative statistical design methodologies for cost-efficient clinical trials, in order to derive reliable results from trials in small population groups, with a particular focus on rare diseases. The project's mission is essentially to provide a systematised, patient inclusive approach to decision-making on benefit risk for new drugs for rare diseases, ensuring cost effective clinical trials and reliable results for small populations. 'Ultimately, this will bring new treatments faster, and treatments that are more reliable to the many patients with a rare disease,' Roes surmises.

> *'We deliver improved and new statistical methods that can substantially improve efficiency of trials and consistency in decision-making on new treatment'*

Roes is well placed to lead the Asterix project, given he was educated as a mathematician and has had a career in both industry and academia. He worked as a statistician and executive in the pharmaceutical industry, which afforded him the opportunity to contribute to new drug treatments for patients. 'It is precisely what motivates me to date: to have an impact on improving the treatment and lives of patients, with such an exact scientific background,' he enthuses.

A BROAD SCOPE

The project is coordinated by the University Medical Center Utrecht, in the Netherlands, but is a collaborative endeavour, involving participation from: Hannover Medical School, Germany; the Medical University of Vienna, Austria; Academic Medical Center, Netherlands; Autonomous University of Barcelona, Spain; Statisticians in the Pharmaceutical Industry, UK; and Vereniging Samenwerkende Ouder- en Patientenorganisaties Betrokken Bij Erfelijkheidsvraagstukken, Netherlands. Roes highlights the broad scope of the project: 'We involved top academic groups, as well as industry representatives in Europe,' he explains. 'We also closely

involve regulatory scientists, ensuring new methods translate into new guidance. And we are not restricted to statisticians, but include paediatric epidemiologists and patient organisations to broaden perspective, as well as ensure patient focus.' The project also made a deliberate choice to engage a number of young PhD students, with a view to creating a new generation of clinical trial statisticians and methodologists, thus ensuring a larger group of experts is available for clinical research in rare diseases.

PATIENT-CENTRIC RESEARCH

In order to address the rights of patients suffering from rare diseases, the project includes patients and patient perspective in its research and clinical trial design. The project is highly innovative in its approach: 'To our knowledge this has never been done before in terms of the development of new statistical methods,' Roes reveals. Key to Asterix is focusing on what matters to patients as, typically, rare diseases have a heterogeneous disease course that is often not taken into account in clinical trial outcomes. 'We have developed patient-centered outcomes (goal attainment scaling) that address this (and hence can also improve efficiency of trials),' Roes explains. The team has also developed, in conjunction with their patient think tank, a pragmatic model of how to include the patient perspective in designing trials, with particular attention to outcome selection.

ENHANCING CLINICAL VALUE

The idea is that the clinical value of trial results will be enhanced by the combined use of pre-clinical data, historical data on disease characteristics, and benefit and risk as perceived by patients to systematically inform and weigh relevant endpoint measures. 'We deliver improved and new statistical methods that can substantially improve efficiency of trials and consistency in decision-making on new treatments,' explains Roes.

Some of the key methodological innovations being developed by the Asterix researchers are: optimising randomisation strategies, new standards of evidence that take into account the rare prevalence of disease, leveraging prior information and the availability of multiple endpoints. This, in turn, enables adaptive designs and meta-analysis using multiple endpoints and proves a blue print to proactively share information on trials in the planning stage. The relevance and clinical value of the newly designed methodological approaches are validated first by cross-testing with available clinical trial data of a range of highly relevant rare diseases and second, by assessing the methods against current and improved regulatory approval strategies.

TAILORED RESEARCH

Roes believes that in order to make progress, it is crucial for researchers and statisticians to step outside their comfort zone. 'Statistical methods to improve efficiency of trials are in principle not unique to small populations, and are well within the 'comfort zone' of statisticians,' he says. 'But rare diseases need special attention to meet numerous challenges.' To do this, in addition to directly involving patients and the patient perspective in the project, the researchers are investigating the widely held standards of evidence, as well as using routes outside the traditional research community to disseminate their findings in order to improve the chances of changing the landscape of drug development for rare diseases.

Clearly, with up to 8000 rare conditions, disease or medical condition-specific guidance is impossible, but the team is taking the specifics of the medical condition into account in order to provide more tailored guidance. The researchers have developed a clustering of rare medical conditions that allows them to give more tailored advice on clinical trial design per cluster. They are then able to 'test drive' the methods they are developing due to the fact their methodology researchers are all within – or associated with – academic medical centres and/or regulatory agencies. 'This is the case for muscle and neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS – trial designs and the patient involvement model), mitochondrial diseases (goal attainment scaling), cystic fibrosis (trial design), and transplantation research and oncology,' states Roes.

OPTIMISING REGISTRIES

There is no doubt this work is set to make a significant contribution to clinical trials for small populations. For example, the methodology used in Asterix will allow patient registry data to be used more effectively and provide the basis to specify information and data to include in registries to optimise their use for trial design and analysis. 'Patient registries are crucial and there are many implemented and under development for rare diseases and information in these registries should be used optimally,' highlights Roes. 'The methods may also allow more formal and robust integration of evidence across the phases of drug development, increasing the efficiency not only of individual trials, but rather drug development programmes.' In addition to publishing their research in peer-reviewed journals and presenting at relevant conferences, the Asterix team presents its results outside the methodology arena, in clinically orientated meetings. 'We also make sure patient representatives are engaged at these meetings, and in general aim for meetings with all stakeholders,' Roes reveals. 'We do so to present our ideas, but more importantly, to put them up for discussion in a broader context.'

Project Insights

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Kit Roes is Professor of Clinical Trial Methodology at the University Medical Center Utrecht in the Netherlands. His focus lies with innovative design and analysis of clinical trials, bridging the gap between clinical trials and real-world evidence. He is chair of the methodology group of the Dutch Medicines Evaluation Board. His experience includes over 20 years of clinical research in the industry and academia, serving as expert and in different senior management positions.

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