Symposium on New Methodology for Clinical Trials in Rare Diseases

Program

Monday September 18th, 2017

13.00h – 13.30h **Opening & Welcome**
by Prof. Kit Roes and Paul Boom (Dutch Ministry of Health)

13.30h – 15.00h **Session 1: Disease clustering to guide trial design and analysis**
Chair: Ferran Torres

Clustering rare medical conditions has guided innovative development of trial design and analysis and will improve efficiency in the development program of orphan drugs. The Asterix clustering is outlined and used to evaluate applicability of novel methods using existing EPARs. Recommendations, specific for different clusters are considered.

Caridad Pontes, MD PhD (Universitat Autònoma de Barcelona)	*Clustering of rare medical conditions based on applicability of methods and designs for clinical trials*
Marian Mitroiu (University Medical Center of Utrecht) Katrien Oude Rengerink, PhD (University Medical Center of Utrecht, CBG)	*Systematic evaluation of the applicability of novel methods to the study of rare medical conditions*
Arantxa Sancho, MD (Instituto de Investigación Puerta de Hierro, Madrid))	*Modelling at a product level as a way to test applicability and move forward to future recommendations*

15.00h – 15.30h **Coffee and Tea Break**

15.30h – 16.45h **Session 2: Fundamental challenges in small populations**
Ethical Framework and patient involvement
Chair: Hanneke van der Lee

This session highlights ethical aspects for drug development in rare diseases, the role of patient engagement in clinical research and an application of the POWER model, a tool for patient engagement in clinical trials.

Prof. Mark Sheehan, PhD (Ethics Advisory Board, University of Oxford)	*Rethinking the ethics of rare disease research*
Kerry Leeson-Beevers (Patient Think Tank, Alstrom Syndrome, UK)	*The role of patient engagement in clinical research*
Charlotte Gaasterland (Academic Medical Center Amsterdam)	*First experiences with the POWER model to involve patient representatives in choosing trial outcome measures*

16.45h – 18.00h **Session 3: Fundamental challenges in small populations**
Correct evidence: the role of randomization and observational data
Chair: Hans Ulrich Burger

Rare diseases with their small populations provide challenges on how to gather correct information of evidence. In this session, the role of randomization and the use of observational data in registries is explored by a forum of clinical, statistical and field experts in dialogue with the public.

Lukas Aguirre (Hannover Medical School)	*A plea to randomization – lessons learned from the case of digoxin*
Martine Jansen-van der Weide, PhD (Academic Medical Center Amsterdam)	*The role of rare disease registries in drug development*
Vincent Gulmans, PhD (Dutch Cystic Fibrosis Foundation)	*Registries do have potential to be used in clinical trials*
Elizabeth Vroom (Patient Think Tank, Duchenne Parent Project)	*A patient perspective (working title, not confirmed)*
David Haerry, PhD (European AIDS Treatment Group)	*Registries and trial data and the real world*

18.00h – 19.00h **Reception**

19.00h – 22.00h **Dinner**

Tuesday September 19th, 2017

8.30h – 9.15h Session 4: Potential and pitfalls of meta-analysis in small populations
Chair: Armin Koch

At the start of the Asterix project, we were optimistic about the use of meta-analysis in small populations. After four years, we have gained a much better knowledge and understanding of the applicability of meta-analysis in drug development for rare diseases. The problem of heterogeneity as well as some practical advice in sparse settings is discussed

Prof. Kit Roes – coordinator Asterix (University Medical Center of Utrecht)	*Meta analysis of a small number of small studies: methods and added value*
Theodor Framke (Hannover Medical School)	*No solution yet – few studies and heterogeneity*
Stavros Nikolakopoulos, PhD (University Medical Center of Utrecht)	*Prospective inclusion of historical efficacy data*

9.15h – 10.15h Session 5: Improving clinical trial design: sequential, multiple endpoints and multiplc treatment comparions
Chair: Gerd Rosenkranz

An overview of new methods developed within the Asterix project leading to improved clinical trial design for small populations is provided. New approaches implemented in clinical studies in ALS and Cystic Fibrosis illustrate the impact in rare diseases.

Gerd Rosenkranz, PhD (Medical University Vienna)	*Advantages of study designs with multiple endpoints or treatment*
Prof. Leonard van den Berg (University Medical Center of Utrecht)	*Methods to combine functional loss and mortality in clinical trials for amyotrophic lateral sclerosis*
Peter van Mourik (University Medical Center of Utrecht)	*A new study design to demonstrate efficacy in cystic fibrosis*

10.15h – 10.45h Coffee and Tea Break & Poster Session

10.45h – 12.15h Session 6: Use of an alternative endpoint in clinical trials
Chair: Hanneke van der Lee

This session starts with a presentation of a regulator's view of the use of alternative endpoints in clinical trials of small populations. Next, it is focused on the measurement instrument Goal Attainment Scaling (GAS), presenting a drug developer's and a patient's view on the use of GAS.

Prof. Kit Roes - coordinator Asterix (University Medical Center of Utrecht)	*Regulatory view on alternative endpoints in clinical trials in rare diseases*
Charlotte Gaasterland (Academic Medical Center Amsterdam)	*Brief introduction to Goal Attainment Scaling*
Edwin Spaans, PhD (Khondrion)	*Why a drug developer is interested in Goal Attainment Scaling*
Radoslaw Kaczmarek, PhD (PTT, European Hemophilia Consortium)	*Goal Attainment Scaling: pinpointing elusive differences in haemophilia therapy effectiveness*

12.15h – 13.15h Lunch

13.15h – 14.30h **Session 7: How to justify different evidentiary standards for decision making in rare disease?**
Chair: Kit Roes

A framework based on prior beliefs to relax the evidence in the target population is presented. Considerations on the total number of patients to be treated as well as using utility functions to support decision making is illustrated. A regulatory view on decision making completes this session.

Prof. Fernando de Andrés-Trelles (Universidad Complutense of Madrid, SAWP-, PDCO-EMA Member)	*Perspective on the minimum evidence to make regulatory decisions*
Nikolaos Zafiropoulos, PhD (Medical University of Vienna)	*Uncertainties and coping strategies in the regulatory review of orphan medicinal products*
Gerald Hlavin, PhD (Sozialversicherungsanstalt Österreichs)	*Leverage existing evidence: evidence, eminence and extrapolation*
Prof. Nigel Stallard (University of Warwick, coordinator INSPIRE)	*A decision-theoretic value of information approach to the design of clinical trials in small populations*

14.30h – 15.00h **Coffee and Tea Break**

15.00h – 17.00h **Session 8: Implementation and Continued Development**

This final session reflects the perspectives of various relevant stakeholders, such as Asterix Advisory Board, young statistical researchers, the Patient Think Tank, regulators and other PF7 consortia on small populations.

Confirmed speakers, among others:
Prof. Josep Torrent-Farnell (Universitat Autònoma de Barcelona)
Prof. Ralf-Dieter Hilgers (University of Aachen, coordinator Ideal),
Prof. Kit Roes (University Medical Center of Utrecht, coordinator Asterix)
Hans Ulrich Burger, PhD (Roche, Advisory Board Asterix)
Prof. Mark Sheehan (University of Oxford)
Marleen Kaatee (president PSC Patients Europe)
Veronica Nederveen (adviser innovation health care at several SME businesses)
Yuki Ando, PhD (PMDA)

17.00h **Closure**

Confirmed Speakers:

Patient Representatives:
Radoslaw Kaczmarek, PhD ** (PTT, European Hemophilia Consortium)
Vincent Gulmans, PhD (Dutch Cystic Fibrosis Foundation)
David Haerry, PhD (European AIDS Treatment Group)
Kerry Leeson-Beevers ** (PTT, Alstrom Syndrome, UK)
Elizabeth Vroom ** (PTT, Duchenne Parent Project)
Marleen Kaatee ** (PTT, PSC Patients Europe)
Veronica Nederveen** (PTT, adviser innovation health care at several SME businesses)

Ethicists:
Prof. Mark Sheehan** (EAB, University of Oxford)

Regulators:
Prof. Fernando de Andrés-Trelles (Universidad Complutense of Madrid, PDCO-, SAWP- EMA)
Arantxa Sancho, MD* (Hospital Universitario Puerta de Hierro)
Katrien Oude Rengerink, PhD* (University Medical Center of Utrecht, CBG)
Marian Mitroiu* (University Medical Center of Utrecht)

Clinical researchers:
Prof. Leonard van den Berg (University Medical Center of Utrecht)
Prof. Josep Torrent-Farnell* (Universitat Autònoma de Barcelona)
Peter van Mourik (University Medical Center of Utrecht)
Edwin Spaans, PhD (Khondrion)
Caridad Pontes, MD PhD* (Universitat Autònoma de Barcelona)
Martine Jansen-van der Weide, PhD* (Academic Medical Center Amsterdam)
Charlotte Gaasterland* (Academic Medical Center Amsterdam)

Coordinators of Asterix, Ideal and Inspire (& statisticians):
Prof. Kit Roes* (University Medical Center of Utrecht, coordinator Asterix)
Prof. Ralf-Dieter Hilgers (University of Aachen, coordinator Ideal),
Prof. Nigel Stallard (University of Warwick, coordinator Inspire)

Statisticians:
Prof. Armin Koch* (Hannover Medical School)
Gerald Hlavin, PhD (Sozialversicherungsanstalt Österreichs)
Stavros Nikolakopoulos, PhD* (University Medical Center of Utrecht)
Lukas Aguirre* (Hannover Medical School)
Theodor Framke* (Hannover Medical School)
Gerd Rosenkranz, PhD * (Medical University Vienna)
Hans Ulrich Burger, PhD ** (Roche)
Nikolaos Zafiropoulos, PhD (Medical University Vienna)

* Asterix Consortium
** Asterix' Patient Think Tank (PTT), Advisory Board (AB) and Ethics Advisory Board (EAB)