DSBS meeting on Extrapolation in paediatrics and use of external data in pivotal clinical trials November 14, 2018

Venue: H. Lundbeck A/S
Agora 5A
Ottiliavej 9
Valby

Professor Franz König from the Medical University of Vienna has been part of developing methods for extrapolation in paediatrics, and has agreed to give two talks on topics where new options for conducting clinical trials in a regulatory setting are expanded.

Agenda:

9:00 -10:00	**Franz König,** Associate Professor, Section of Medical Statistics, Medical University of Vienna: **Adaptive paediatric investigation plans – how to exploit extrapolation in drug development for children**
10:00-10:15	Break
10:15-11:00	**Franz König,** Associate Professor, Section of Medical Statistics, Medical University of Vienna: **Beyond RCTs - using historical data in pivotal clinical trials**

Registration

Deadline for registration: November 5

The meeting is free, but please register, so we can prepare access cards in advance.

To register, please send a mail to commres1351@Lundbeck.com

Abstracts:

Adaptive paediatric investigation plans – how to exploit extrapolation in drug development for children

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 (PIP) should be agreed on in early phases of drug development in adults. A full independent drug development programme to demonstrate efficacy may not be ethical and/or feasible in such a highly vulnerable population as children. Here, extrapolation [1] from adults to children can be 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 [2] 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. However, such an adaptive PIP would require some more flexibility from both regulatory authorities and sponsors. We will discuss how an adaptive PIP would fit considering the EU legislation and its implementation in EMA procedures. Furthermore, frequentist and Bayesian approaches [3] for extrapolation are discussed.

[1] EMA Draft Reflection paper on the use of extrapolation in the development of medicines for paediatrics (2017). EMA/199678/2016. European Medicines Agency, London, UK.
[2] Bauer, P., & König, F. (2016). Adaptive paediatric investigation plans, a small step to improve regulatory decision making in drug development for children?. *Pharmaceutical Statistics*, *15*(5), 384-386.
[3 Hlavin, G., Koenig, F., Male, C., Posch, M., & Bauer, P. (2016). Evidence, eminence and extrapolation. *Statistics in Medicine*, *35*(13), 2117-2132.

Beyond RCTs - using historical data in pivotal clinical trials

Randomized controlled trials (RCTs) became the standard for establishing the efficacy of a new treatment. But how to generate sufficient evidence for drug approval if fully powered RCTs are not feasible, as for example, when there is a high unmet medical need, in rare diseases or the development of personalized therapies. Recently, data transparency initiatives have re-shaken the landscape of medical research by granting access to raw data (on individual patient level). This opens new opportunities and raises the question whether to incorporate historical data more prominently in drug development when determining efficacy for new medicines in difficult situations. We propose a new framework for evidence generation, which we call "threshold-crossing." This framework leverages the wealth of information that is becoming available from completed RCTs and from real world data sources. Relying on formalized procedures, information gleaned from these data is used to enable efficacy assessment of new drugs for carefully selected situations. We will discuss the benefits and caveats of "threshold-crossing" compared to more traditional approaches in terms of type I error rate, power and sample sizes.

Paper: https://ascpt.onlinelibrary.wiley.com/doi/abs/10.1002/cpt.515