EMA
EUROPEAN MEDICINES AGENCY

Methodology Working Party (MWP) Interested Parties Meeting

7 June 2024 (09:00-13:00)
Virtual meeting only, via Teams (pre-registration required)

The aim of this regular Interested Parties meeting is to give stakeholders the opportunity to raise and share reflections on relevant methodological topics with the Methodology Working Party (MWP) and to engage in discussions with members of the MWP and the Methodology European Specialised Expert Community (Methodology ESEC). The insights shared by stakeholders will help the MWP identify potential gaps in their workplan and prioritize its guideline development accordingly.

Following a call for topic proposals, MWP has selected topics for discussion. Topics not selected for this meeting may be addressed in future meetings.

While the floor will be given to the stakeholder associations who are presenting, the meeting is open to all Interested Parties who can join in listening mode preceding a registration shared via their stakeholder associations.

08:45 Joining and technical checks

09:00 Welcome and opening

Welcome and opening remarks from the MWP Chairs **10'**
Kit Roes *and* ***Kristin Karlsson*** *(MWP Chair and Vice-chair)*

09:10 MWP updates

Updates on MWP workplan **10'**
Kit Roes *(MWP Chair)*

Interaction of MWP and BDSG **10'**
Kristin Karlsson *(MWP Vice-chair)*

09:30 Session 1

Session Chairs: ***Florian Lasch*** *(EMA)*

Discussants: ***Florian Klinglmueller*** *(MWP)****, Juan Jose Abellan Andres*** *(EMA)****, Andreas Brandt*** *(BfArM)****, Lukas Aguirre Dávila*** *(SAWP)*

Causal inference in clinical trials **10'**
Sanne Roels *(Johnson & Johnson), EFSPI*

Causal inference methods rely on the concept of "counter-factual" outcomes, which frequently rely on unverifiable assumptions and could hence be considered as controversial by regulators.

Covariate adjustment in randomised clinical trials **10'**
Henrik Ravn *(Novo Nordisk), EFPIA & EFSPI*

Adjusting for covariates in randomized clinical trials presents opportunities to improve statistical efficiency for estimating and testing treatment effects while having minimal impact on bias and type I error rate.

Recent assumption lean methodological advances have paved the way for boosting the precision when estimating marginal causal effects in RCTs. Concrete methods include Targeted maximum likelihood for robust and efficient utilization of prognostic baseline covariates.

Multiplicity adjustments in multi-armed trials with inferentially independent hypotheses **10'**
Tobias Mielke *(Johnson & Johnson), EFPIA*

Recent publications and the FDA draft guidance pointed to no need for FWER control in platform trials for situations, in which two independent treatment arms are compared to a common control arm. Still, uncertainty on applicability of this exists in conventional multi-armed trials with independent research hypotheses, conducted by a single sponsor.

Designing clinical trials with a delayed treatment effect **10'**
Dominic Magirr *(Novartis) &* ***Carl-Fredrik Burman*** *(AstraZeneca), EFPIA*

Delayed treatment effect (e.g., delayed separation of survival curves) is often observed in cancer immunotherapy clinical trials. Due to the violation of proportional hazards assumption, the power of the usual log-rank test can be considerably reduced at detecting a delayed treatment effect. How to account for

delayed treatment effect in the design, analysis and interpretation of clinical trials poses many challenges and is a critical area of interest to trial practitioners.

Meta-analyses and the estimand framework **10'**
Christian Pipper *(Novo Nordisk) &* ***David Wright*** *(AstraZeneca), EFSPI*

The estimand framework could potentially provide a more formalized and standardized framework for aligning trials that are to be used in a subsequent meta-analysis.

Discussion **40'**
EFPIA, EFSPI and EU regulators

11:00 Break 15'

11:15 Session 2

Session Chair: ***Andrew Thomson*** *(EMA)*

Discussants: ***Elina Asikanius*** *(MWP),* ***Florian Klinglmueller*** *(MWP),* ***Lukas Aguirre Dávila*** *(SAWP),* ***Flora Musuamba Tshinanu*** *(MWP, SAWP)*

Augmented controls in the confirmatory setting **10'**
Marc Vandemeulebroeke *(UCB), EFSPI*

The ACT-EU Multi-Stakeholder workshop in Nov '23 highlighted the need for guidance on the role (if any) of augmented controls / Bayesian borrowing / integrated evidence in the confirmatory setting.

Synthetic control arm in clinical trials for regulatory and HTA/reimbursement decision making **10'**
Björn Holzhauer *(Novartis), EFPIA*

Industry would like to understand further the guidance and examples on the what 'good' synthetic control arm (SCA) clinical trials look like to enable regulatory and HTA decision making; once it is decided that SCA is the appropriate and best route to provide evidence given the specific situation, what would be the best approach to conduct such studies? What are the common challenges and pitfalls that need to be aware of and to avoid?

Dynamic borrowing for clinical trials **10'**
Roel Straetemans *(Johnson & Johnson), EFSPI*

Borrowing of external data using dynamic Bayesian approaches is considered in rare indications to support claims on efficacy of novel interventions. Discussions in the November ACT EU workshop did not address the question on "how to borrow, if you must". A discussion on "exceptionally" acceptable design & analysis methodology (and requirements) could help alleviate some uncertainties and result in larger consistency of submitted designs.

Extrapolation across related diseases **10'**
David Wright *(AstraZeneca), EFSPI*

Extrapolation frameworks have recently been established by major health authorities incl. EMA. So far, they have mainly been applied to paediatric extrapolation. Extrapolation across related diseases is less well understood and regulated, but also highly relevant, especially for rare diseases or diseases with ambiguous taxonomy.

Dose recommendations across related indications **10'**
Marina Savelieva *(Novartis), EFSPI*

Despite growing understanding on disease pathways and targets in multiple indications (e.g. PSO/PsA), uncertainties on the appropriateness of pharmacometric modelling for informing dose decisions across indications is prevalent, leading to possibly inefficient drug development programs.

Discussion **40'**
EFPIA, EFSPI and EU regulators

12:45 Closing remarks

Closing remarks by the MWP Chairs **15'**
Kit Roes *and* ***Kristin Karlsson*** *(MWP Chair and Vice-chair)*

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