EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Regulatory update
Methodology Working Party – with a focus on statistics

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Chair

The views expressed are personal views and not necessarily the views of CBG-MEB or EMA.

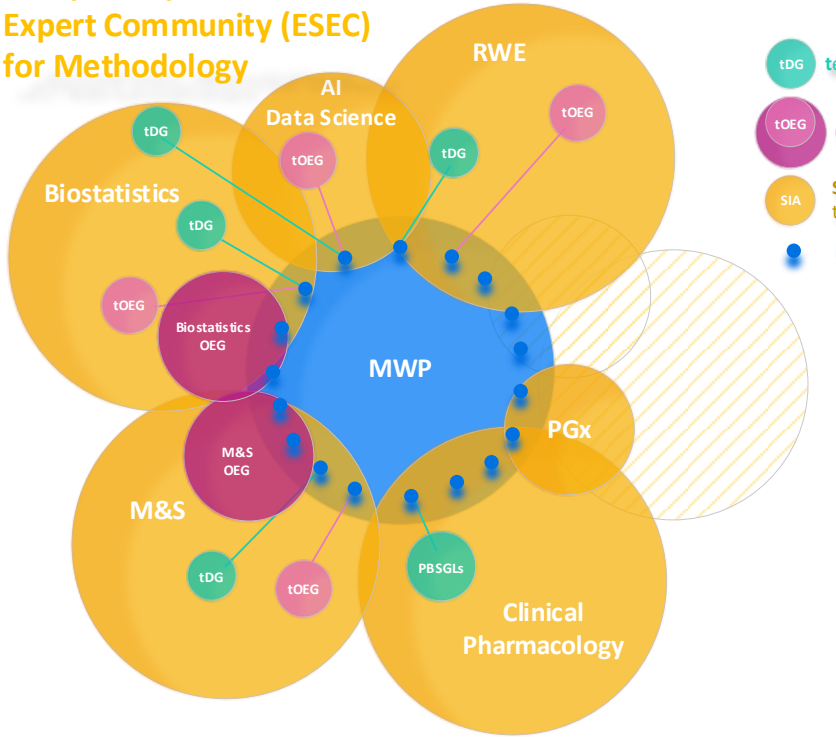
Key tasks of the MWP

- Providing **product-related support** when requested by EMA Committees and the Scientific Advice Working Party.
- **Preparing, reviewing and updating** guidelines and concept papers.
- **Engaging with stakeholders.**
- **Develop the EMRN methodology competence** and provide training and workshops to assessors.

23 members based on experience in Biostatistics, M&S, Clinical Pharmacology, RWE, Pharmacogenomics, AI & Data Science **meeting every 2 weeks**

European Specialised Expert Community

European Specialised Expert Community (ESEC) for Methodology



ESEC members by SIA	N
RWE	91
Biostatistics	83
Clinical Pharmacology	73
AI & Data Science	61
M&S	54
PGx	26
Total	202

Regulatory update

- Recent guidances and highlights on content.
- Ongoing & new rolling workplan 2025 – 2028.
  - Emerging themes for methodological development.
- Collaboration across the product life-cycle.
- Interactions.

Recent guidelines and highlights on content

Reflection paper on establishing efficacy based on single arm trials submitted as pivotal evidence in a marketing authorisation application.

Adopted PROM/CHMP 9 September 2024

- SAT as trial standing on its own: Considerations of external ”control” not included.
- ICH E9 (R1) more rigorously included (counterfactual treatment condition, intercurrent events, definition of treatment initiation,…).
- HTA perspective (implicitly) included: other research questions, data needed on other endpoints & covariates (in view of patient relevance & indirect comparisons).

Recent guidelines and highlights on content

Reflection paper on the use of artificial intelligence in the lifecycle of medicines.

Adopted PROM/CHMP 9 September 2024

- General principles across the life cycle.
- A risk-based approach with precise delineation of regulatory risk in view of AI Act context.
- Essential part of the Artificial Intelligence Workplan to guide use of AI in medicines regulation.
- Multidisciplinary drafting group – with valuable input from statistics, pharmacometrics and covering Human and Veterinary.

Recent guidelines and highlights on content

Data Quality Framework.

Reflection paper on use of real-world data in non-interventional studies to generate real-world evidence (*public consultation closed 31/8/2024*).

- Multidsiciplinary across pharmaco-epidemiology, statistics, etc.
- Structured according to the primary research question of interest, which can be causal.
- Estimand framework as well as key elements originating in causal inference context (e.g., target trial) included.

Ongoing & new rolling workplan 2025 – 2028.

Ongoing Biostatistics…..

- Bayesian Concept Paper – Stakeholder workshop to be held.
- Platform Trials Reflection Paper.
- Multiplicity Guideline update.
- Revision of Non-inferiority / Switching guidelines.
- Q&A on small populations, including indirect comparisons.

- *MWP full review of SmPC guidance (public consulation closed).*

Ongoing & new rolling workplan 2025 – 2028.

Platform Trials Reflection Paper

Multiplicity Guideline update

MWP full view on SmPC guidance (public consulation closed)

- Fundamental considerations on Type 1 Error Control as instrument for controlling risks in regulatory decision making. Well understood and fundamental for single confirmatory studies, more challenging in complex designs and “across study” decision making.
- Primary assessment of efficacy, secondary assessment (of properties) once efficacy is confirmed and communication (through SmPC) are not one size fits all.

Stakeholder input to new 2025-2028 workplan

Causal inference in clinical trials

Covariate adjustment in randomised clinical trials

Multiplicity adjustments in multi-armed trials with inferentially independent hypotheses

Designing clinical trials with a delayed treatment effect

Meta-analyses and the estimand framework

Augmented controls in the confirmatory setting

Dynamic borrowing for clinical trials

Extrapolation across related diseases

Dose recommendations across related indications

Workplan: To start 2025

Multidisciplinary (selected)

Concept Paper on the use of external controls (priority)

(i) External control *by design* (prospective, fully in clinical trial protocol).

(ii) External control data added post-hoc to initial trial (SAT or other).

Q&A to be read in conjunction with the baseline covariates guideline to take into account the use of synthetic covariates.

Q&A on PBPK modelling

Concept Paper on Model informed bioequivalence and biosimilarity.

Workplan: To start 2026-2027 (preliminary)

Multidisciplinary

Q&A on the use of synthetic data in regulatory submissions.

Use of modelling& simulation in bioequivalence.

Concept Paper on the use of the credibility matrix framework for decision making.

Concept Paper on the use of pragmatic trials in regulatory decision making.

Workplan: To start 2026-2027 (preliminary)

Biostatistics

Revision of Adaptive Designs to take into account outputs of ICH E20.

Guidance on how to align estimand attributes across different trials in the context of a meta-analysis.

Collaboration across the product life-cycle

Evidence generation throughout the lifecycle.

- Initiated coordination in Methodology guidance development across EMA MWP, CTCG and HTA CG Subgroup on Methodology.
- Webinar (July 2024) and Workshop (fall 2024) on "Uncertainty" across market authorisation and HTA/Reimbursement.

First connections made to new FDA CDER Quantitative Medicine Center of Excellence.

https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cder-quantitative-medicine-center-excellence-qm-coe

MWP Chairs, Members and EMA directly engaged in Horizon Europe and IHI projects to innovate (ERAMET, INVENTS, RealiseD).

Interactions

In the interest of patients and society as a whole….

……..ensure……novel approaches meet ……. evidentiary standards….. as well as improve quality and efficiency of drug development.

- A shared responsibility as supported by more intensive stakeholder interactions.
- The pace & diversity of proposed innovation is at odds with building real life experience.
- To truly foster the right innovations – it needs a (more?) honest conversation.

- Statisticians may actually show leadership here…….

Any questions?

Further information

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