EMA
EUROPEAN MEDICINES AGENCY

# Navigating priorities from regulatory perspective

## For pharmaceutical statistics and statisticians

## Methodology Working Party

EFSPI September 2025

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

# EMA Methodology Working Party

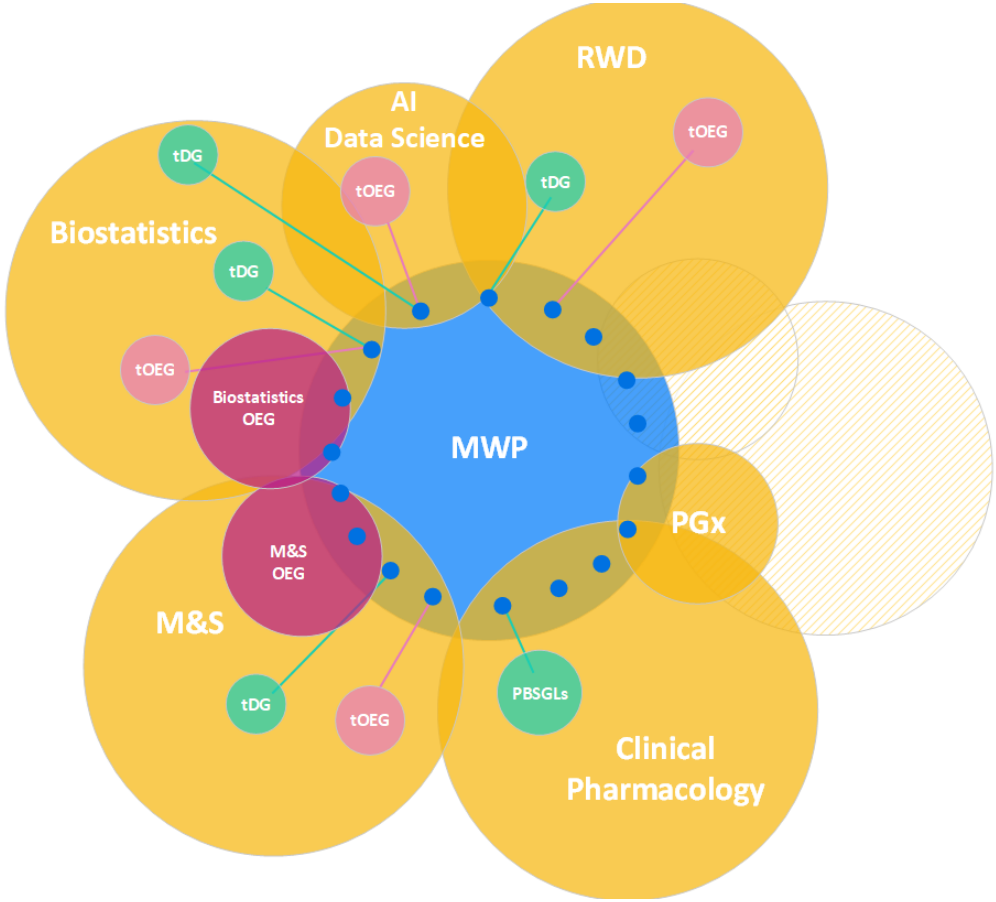


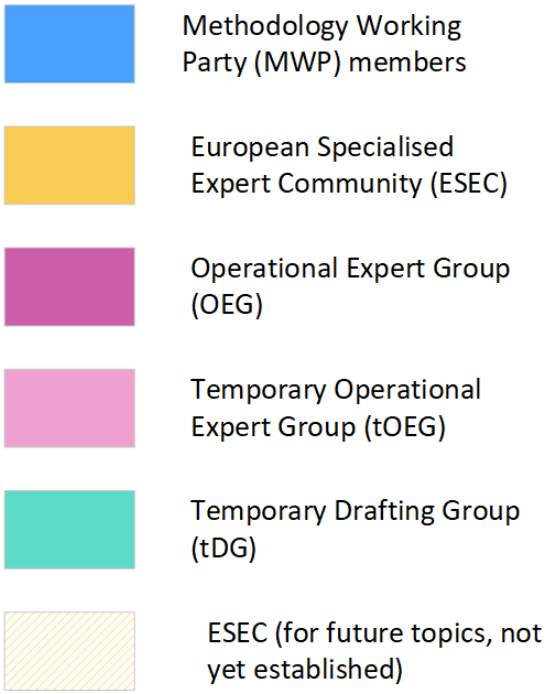


“Best methodological practice in assessment and produce credible model-based evidence that supports medicine development and regulatory decisions.”

Longer term: Quantitative evidence framework to assess uncertainty when multiple sources of data are integrated, including the use of modelling and AI for such integration.

# MWP and its Expert Community (ESEC)

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**76** AI & Data Science

**96** Biostatistics

**82** Clinical Pharmacology

**70** Modelling & Simulation

**34** Pharmacogenomics

**103** Real World Data

**248** Methodology ESEC members

(as of July 2025)

# Navigating priorities

The regulatory update of 2024…..

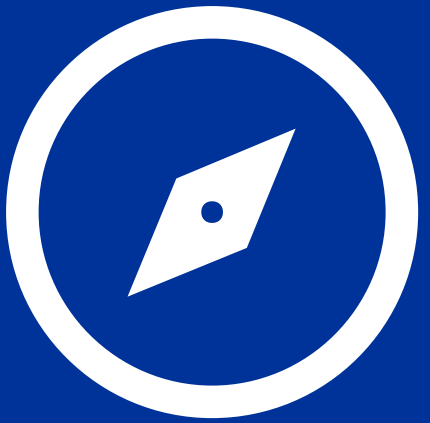
A few relevant developments

Estimands implementation (1 slide……)

Evidence generation

Expanding the horizon

Communication & Interaction



# A few relevant developments

Network Data Steering Group

ACT-EU

The new Pharma Legislation

**Artificial Intelligence in European Medicines Regulation: From Vision to Action. Harnessing the Capabilities of Artificial Intelligence for the Benefit of Public and Animal Health**

Luis Correia Pinheiro[1,*], Peter Arlett[1], Kit Roes[2], Flora Musuamba Tshinanu[3], Gabriel Westman[4], Zaide Frias[1], Hilmar Hamann[1], Joaquir … Jeppe Larsen[6], Karl Broicl

PERSPECTIVE

**Clinical Evidence 2030**

Peter Arlett[1], Denise Umuhire[1,*], Patrice Verpillat[1], Paolo Foggi[2], Ulla Wändel Liminga[3], Bruno Sepodes[4], Marianne Lunzer[5], Brian Aylward[6], Spiros Vamvakas[1], Kit Roes[7], Frank Pétavy[1], Steffen Thirstrup[1], Maria Lamas[8], Emer Cooke[1] and Karl Broich[9]

# Estimands implementation

Clinical guidelines

Learning from experience across MAA & HTA

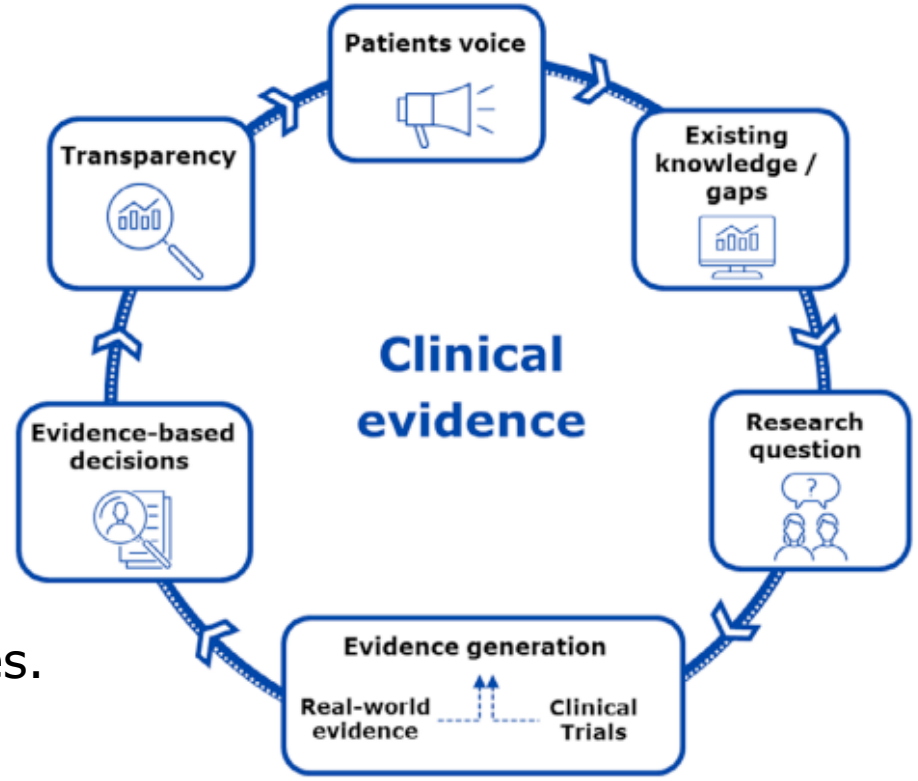
Confirming efficacy, hypotheses testing, estimands, estimation?

# Evidence generation

The majority of regulatory guidances addresses **single experiments / data sources / areas /.. within the drug developmeny life cycle**, in the context of regulatory decision making.

**Important to rely on basic scientific inference principles**.

**Important to improve** in light of increased understanding of disease, technological advancement & new treatment modalities.




Guideline on **predictive biomarker assay development** in the context of medicinal product lifecycle

**ICH M18** - Framework for Determining Utility of Comparative Efficacy Studies in Biosimilar Development Programs

Concept paper on the use of **pragmatic trials** in regulatory decision making

Q&A on the use of real-world data including **patient registries** for regulatory purposes

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# Evidence generation

Going beyond the (prospective) individual experiment **is a fundamental step in scientific inference.**


Augmenting control groups in RCTs, digital twins, Bayesian borrowing, external controls, platform trials leveraging non-concurrent controls, model based extrapolation of adult to pediatric data,……


Moves us essentially into meta-analysis, evidence synthesis, indirect comparisons, while reducing the amount of prospectively collected data.

**Strategic priority to achieve the benefits: Progress fundamentally and coherently.**

EFSPI Workshop 2019
Oekolampad Church

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# Example: Single arm trial & external data

9 September 2024
EMA/CHMP/458061/2024
Committee for Medicinal Products for Human Use (CHMP)

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

Considerations on evidence from single-arm trials

## Abecma original CMA

CAR- T cell therapy in patients with relapsed and refractory multiple myeloma.

Adult patients with relapsed and refractory multiple myeloma who have received at least **three** (*two*) prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.

## Open-label single-arm Phase 2 study.

Primary objective to evaluate efficacy, defined as ORR of ide-cel in subjects with RRMM.
Alternative hypothesis: ORR is > 50%, with a target ORR of 70%.
Total enrolled: 140
Ide-cell treated: 128

# Example: Single arm trial & external data

**Real World Data study added to submission package (CMA)**

Study NDS-MM-003 was a global, non-interventional, retrospective study set up to generate an external comparison arm for study MM-001. Data from sources including clinical sites, registries, and research databases were collated in a single data model, and further analysed.

Leading to 190 matched subjects

Primary endpoint ORR (at least PR); Secondary included DoR, PFS and OS

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# Example: Single arm trial & external data

1. This is not an external control arm – it **is secondary use of data** from both the SAT and the real world data sources.

2. In addition to data quality & potential bias in data selection: detailed **modelling of the data generating mechanism across trial and external data** is core to statistical inference.

3. It is not always transparent or self evident which assumptions are needed to ensure that probability statements made (e.g., in confidence intervals for treatment effect parameter(s)) are (in a sense) “correct”.

Note: This Phase II SAT was followed by a RCT in almost the same population…..

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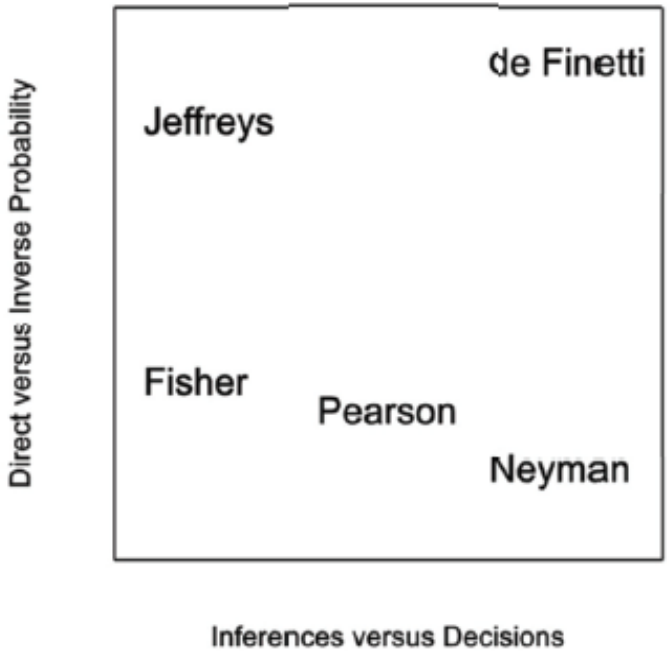
# Evidence generation

- There is no universally superior system of statistical inference (yet).
- **Statistical inferential approach to fit the research question.**
- Use of Bayesian methods ≠ Bayesian inference.




- In regulatory **confirmatory** thinking, emphasis has been on Neyman-Pearson based "Decisions": The "decision" that the trial confirms clinical efficacy.
- **T1 Error control for confirmatory trials** is (for now….) a design feature at the (individual) trial level.

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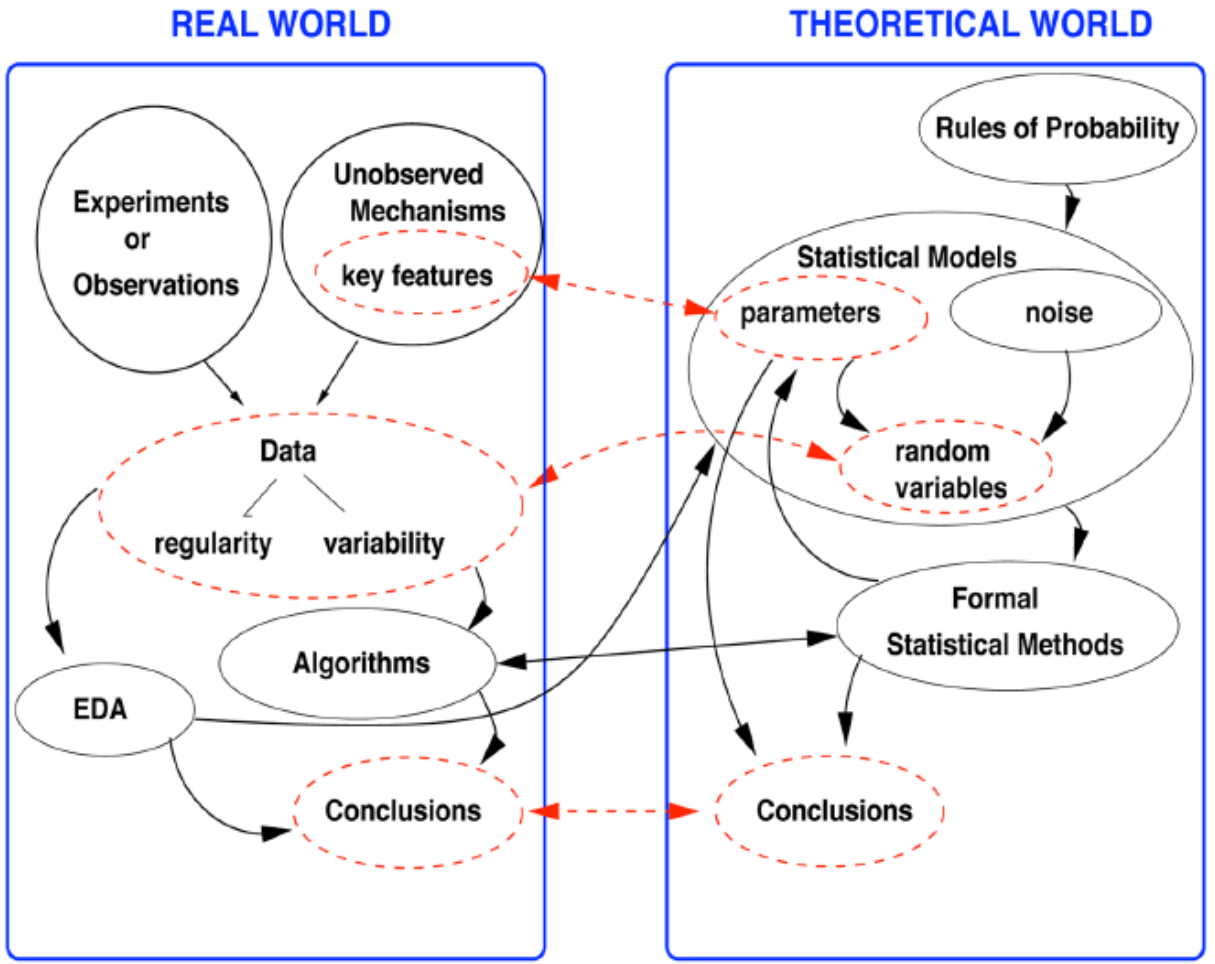
# Evidence generation

- Data are modelled through systematic elements and probability distributions.
- Data serve to reveal characteristics of underlying system that generated the data (**data generating mechanism**).
- Formal inference serves to draw *conclusions* about the unknown parameters.




Published in final edited form as:
*Stat Sci.* 2011 February 1; 26(1): 1–9. doi:10.1214/10-STS337.

**Statistical Inference: The Big Picture**

**Robert E. Kass**[*][Professor]
Robert E. Kass: kass@stat.cmu.edu

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# Evidence generation

Concept paper on *the use of the* **evidence assessment framework** for decision making

Guidance addressing integrating evidence:

- ICH 11A Pediatric extrapolation.
  - Significant effort to support harmonised implementation.

- ICH M15 Model Informed Drug Development.

Translate to operational, verifiable criteria that allow assessing credibility that is fit to the research question and context of use.

Route to more principled approach for complex trial designs in addition to T1E control.

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# Evidence generation: Data science and AI

## Data Science & Artificial Intelligence (AI)

Regulatory guidance on AI/ML use across the medicinal product lifecycle,

- **Standardisation of terminology and principles (with FDA, PMDA).**
- Use of AI in clinical development.
- Use of AI in pharmacovigilance (with PRAC).

## Data management and analytical capability

Strengthening the network's data analytics capabilities - aims to generate high-quality evidence using both established and novel methods


AI fundamentally different modelling (at least some).

Data & AI are already impacting the process of regulatory assessment.

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# Expanding the horizon

If we look on the short term:

| | Ongoing | To be initiated in 2026 | To be initiated later |
|---|---|---|---|
| **Biostatistics** | Reflection Paper on the **use of Bayesian methods** in clinical development<br>Reflection Paper on **platform trials**<br>Revision of the guideline on **multiplicity issues** in clinical trials<br>Guideline on **non-inferiority and equivalence comparisons** in clinical trials<br>Q&A on **small populations**, including Q&A on **indirect comparisons** | Revision of the guideline on **missing data** in confirmatory trials to implement ICH E9 (R1)<br>**Workshop on multiplicity**<br>**Training on statistical methodology applied at quality level** | Revision of **adaptive designs** guidance to take into account ICH E20<br>Guidance on how **to align estimand attributes** across different trials **in the context of a meta-analysis** |

# Expanding the horizon

If we look on the long term:

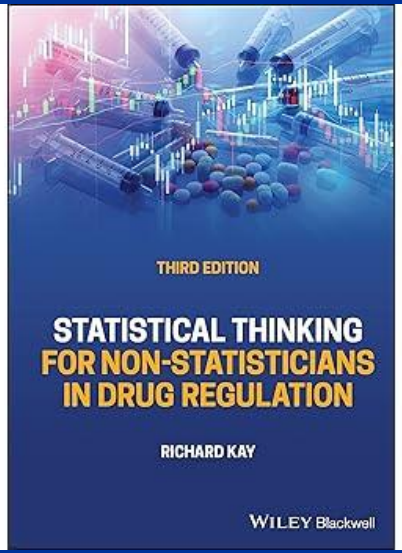
| | Ongoing | To be initiated in 2026 | To be initiated later |
|---|---|---|---|
| **Multi-disciplinary** | Concept paper on the development of a reflection paper on the use of **external controls** for evidence generation in regulatory decision-making | Reflection paper on the use of **external controls** for evidence generation in regulatory decision-making | Concept paper on the use of the **evidence assessment framework** for decision making |
| | **Workshop on use of external controls** | Guidance on assessment and reporting of **mechanistic models** used in the context of model-informed drug development — BS, CP, M&S | Q&A on model-informed **dose finding/selection** — BS, M&S |
| | | Q&A to be read in conjunction with the baseline covariates guideline to take into account the use of **synthetic covariates** | Q&A on the use of **synthetic data** in regulatory submissions |
| | | Q&A on **PBPK modelling** — CP, M&S | Concept paper on the use of **pragmatic trials** in regulatory decision making — BS, RWE |
| | | | Guidance on **missing data in non-interventional studies** — BS, RWE |
| | | | Guidance on use of **modelling & simulation in bioequivalence** — CP, M&S |
| | | | Guidance on the clinical pharmacology of **peptides** — CP, M&S |
| | | Workshop on model informed bioequivalence and model-informed approaches for bridging across formulations | |

# Expanding the horizon

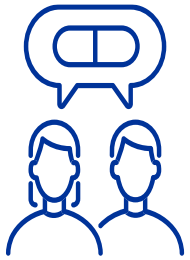
Statistical thinking increasingly important and impactful beyond late stage clinical development:

Ranges from biosimilar development (Quality Assessment), post-marketing real world data studies to use of AI across the life cycle.

Needs different perspectives, additional skills and different mind sets.

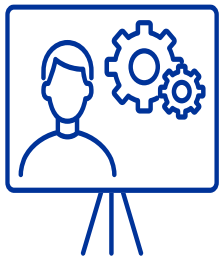


# Communication

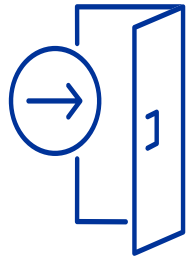


- Interested parties' meeting

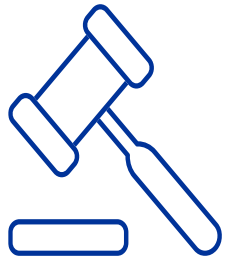
- EU-funded research projects



- ACT EU and NDSG workshops



- Open-source software



- Pharmaceutical legislation

# Communication

- I utical p m

Regulatory assessment: much more than confirming primary efficacy.
Treatments reaching patients: requires (even) more.

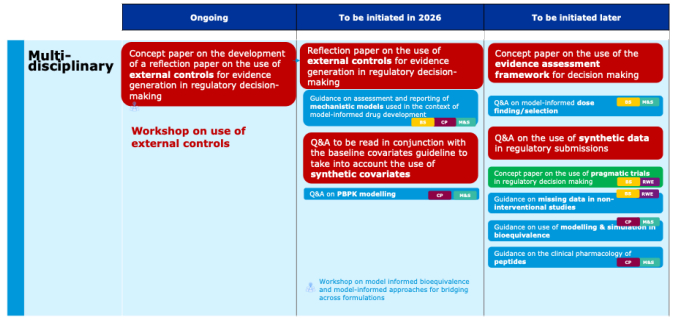
Clinical trials: need to be able to provide relevant and reliable estimates of treatment effects and their uncertainty (SmPC).

This turns out to be:

- A far from trivial problem in more complex designs or proposed multiple testing strategies in “simple” trials.
- A problem largely neglected at the design stage.

# Interaction

The Methodology Working Party benefits increasingly from cross-disciplinary work & learning.

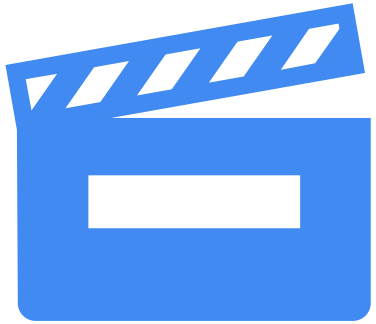



This is not without challenges……

It is not yet matched in interactions with stakeholders:

- Stakeholder feedback on MWP Workplan is dominated by statisticians.

**Given strategic priorities: Could a similar development follow in industry partners?**



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# Concluding

Continuous improvement of core evidence generation (individual experiments, trials,..) leveraging increasing knowledge and improving technology.

Towards a principled and model based approach for evidence generation when combining data across experiments or data sources.

Design with the end in mind: relevant and reliable evidence to inform decision makers, healthcare professionals and patients.

Embrace cross-disciplinary collaboration and learning within the methodology domain.