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Committee for Medicinal Products for Human Use (CHMP)/Methodology Working Party (MWP)

Concept Paper on the Development of a Reflection Paper on the Use of External Controls for Evidence Generation in Regulatory Decision-Making

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1. Introduction

Randomised controlled trials are the gold standard of evidence to support causal conclusions on the benefits and risks of medicines in regulatory decision making along the lifecycle.

However, in some situations, causal conclusions may be derived from a setting where the investigational medicinal product data was collected under a clinical trial protocol while the control arm (counterfactual in the causal claim) was not a randomised arm in that same protocol. In these situations, a so-called external control, may be derived from data from other clinical trials, real-world data (RWD) or other data sources.

Although various guidance exists on topics pertinent in this area (see, i.e. [1] – [8]), specific regulatory guidance on the use of external controls to support regulatory decision making in Europe is currently lacking.

2. Problem statement

Recent developments in data availability and statistical/pharmacoepidemiological methodology have led to an increase in proposals using external controls to support regulatory decision making.

However, further reflection on the methodological reliability and operational aspects of such approaches is needed.

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Acknowledging that a standard definition of external controls is currently not available, this will be addressed in the reflection paper.

The reflection paper will outline general principles for assessing when external controls could be appropriate for regulatory decision making.

3. Discussion (on the problem statement)

The aim of the reflection paper is to describe the main challenges with external controls and further discuss the circumstances and methodological constraints under which the use of external controls could be considered appropriate for generating pivotal or supportive evidence, either for efficacy, safety or other relevant regulatory decision-making objectives. The reflection paper will discuss the following aspects:

- Clarification of terminology (e.g., definition of an external control, synthetic data, digital twins, historical data, etc.)
- The appropriate clinical and regulatory setting and minimal requirements for external controls
- Replication and reproducibility of results
- Operational and feasibility aspects
- Planning, conduct, and reporting of externally controlled studies, including the use of the ICH E9(R1) estimand framework to clearly define the causal question and the use of target trial emulation to align study design and analysis with the specified estimand and reduce bias, as well as associated statistical considerations such as sample-size determination and type I error control. Prospectively planned external control comparisons vs comparisons conducted when results are already available (either trial data, external control or both)
- Data quality: relevance, reliability, extensiveness, timeliness
- Source(s) of the external data
- Individual patient level data, (semi-)aggregated data

There are other potential uses of external data which are out of scope of this concept paper, for example:

- Use of historical data for contextualisation (e.g., to understand the clinical context by describing standards of care, variability in clinical practices and unmet medical needs). Related aspects have already been addressed in existing guidance [2].
- External control data used to augment randomised controlled trials. As this regards a fundamentally different clinical and regulatory setting in which random allocations to control are possible and the methodological aspects are specific to augmentation, these designs will be discussed in other regulatory documents under development.
- Indirect comparisons using a network meta-analysis. These are usually based on comparisons of results between randomised controlled trials which is beyond the scope of this reflection paper. They are conducted within fundamentally different clinical and regulatory settings with methodological aspects that are specific to network meta-analyses.

While these approaches are outside the scope of this Reflection Paper and are therefore not discussed in detail, this does not imply that guidance is not necessary. Several principles relevant

to externally controlled studies, such as the need for exchangeability across data sources and compatibility of measurements, remain pertinent in these other contexts.

4. Recommendation

MWP recommends drafting a reflection paper on the use of external controls for evidence generation in regulatory decision-making to address the points outlined above.

5. Proposed timetable

Establishment and endorsement of temporary Drafting Group (tDG) in Q2 2026.

Discussion of draft reflection paper at the Committee for Medicinal Products for Human Use (CHMP) in Q4 2026 followed by 3-months public consultation. Finalisation and adoption by CHMP expected by Q2 2027.

6. Resource requirements for preparation

A tDG, co-led by 2 MWP members and consisting of experts from the European Specialised Expert Community (ESEC) for Methodology to be established. Additional expertise from the Scientific Advice Working Party (SAWP), the CHMP, the Pharmacovigilance Risk Assessment Committee (PRAC) and relevant clinical Working Parties would be envisaged for the tDG. Regular discussions with and adoption by MWP are planned.

The tDG meets regularly and the meeting format and frequency is adapted to the drafting process.

7. Impact assessment (anticipated)

The reflection paper will enhance the understanding of methodological concepts and challenges. It will outline criteria for the potential acceptance of the use of external controls and aspects to be taken into account at the planning, conduct and reporting stages. It will allow for consistent assessment and ultimately support better informed decision making.

8. Interested parties

Guidance on this topic is expected to be important to the following Committees and Working Parties who should hence be closely engaged in the drafting stage: CHMP, SAWP, the Committee for Advanced Therapies (CAT), the Committee for Orphan Medicinal Products (COMP), the Paediatric Committee (PDCO), the Oncology Working Party (ONC WP), and PRAC.

As the reflection paper is of relevance for the Clinical Trials Coordination Group (CTCG) and HTA bodies, they will be kept informed regularly on the developments on this topic.

As any guidance will be of high relevance to Industry stakeholders, academics, patients and health care professionals, their views will be taken into consideration during the public consultation phase.

9. References to literature, guidelines, etc.

[1] ICH E9 Statistical principles for clinical trials, published in 1998.

[2] Reflection paper on use of real-world data in non-interventional studies to generate real-world evidence (Reference number: EMA/99865/2025), published in 2025.

[3] Guideline on registry-based studies (Reference number: EMA/426390/2021), published in 2021.

[4] Data Quality Framework for EU medicines regulation (Reference number: EMA/326985/2023), published in 2023.

[5] Reflection paper on establishing efficacy based on single-arm trials submitted as pivotal evidence in a marketing authorisation application (Reference number: EMA/CHMP/430688/2024), published in 2024.

[6] Clinical trials in small populations (Reference number: CHMP/EWP/83561/2005), published in 2006.

[7] ICH E10 Choice of control group in clinical trials, published in 2001.

[8] ICH E11A Guideline on paediatric extrapolation, published in 2024.