Fimea
Lääkealan turvallisuus- ja kehittämiskeskus

Motivation for planned reflection paper and outline of aspects to be addressed

Elina Asikanius on behalf of Olaf Klungel and myself

Statistician, MWP and SAWP member

11.11.2025

Why are we working on an external controls RP?

- We receive external control proposals in all shapes and forms
- These rarely lead to the desired outcome for any party involved

→ Prioritized in the MWP workplan for 2026

- A framework for how we can do better
  - Consistency in regulatory assessment and decision making

  → Support for assessors, committees and working parties
  - Transparency in outlining our expectations to industry

  → Support for industry
- Aspiration that this will lead to increased transparency, right-level of detail in planning and reporting and good quality submissions
- …and maybe eventually to less (unsuccessful) proposals

How are we working on the RP?

- Joint effort within the MWP: biostatistics and RWD/pharmacoepidemiology domains
- For a helpful RP we need fundamental understanding of clinical trials, current evidence standards for regulatory decision making, variability in questions of interest in regulatory decisions making, methodological issues in clinical trials, data generating mechanisms, data sources, epidemiology methods and how these compare to traditional biostats, and much more
- Support from a drafting group: NCAs and EMA with varied experience and expertise

How are we working on the RP?

- MWP co-leads:
  - Elina Asikanius (statistician)
  - Olaf Klungel (pharmacoepidemiologist)

  + Ina Rondak

Core drafting group for CP

- Volunteers from the ESEC:
  - Angelika Geroldinger (AGES, statistician)
  - Andrei Barbulescu (EMA, pharmacoepidemiologist)
  - Susanne Urach (AGES, statistician)
  - Aysun Cetinyurek Yavuz (MEB, statistician)
  - Frauke Naumann-Winter (BfArM, clinical/rare diseases)
  - Martin Posch (Med Uni Vienna, statistician)
  - Andreas Brandt (BfArM, statistician)
  - Juanjo Abellan (EMA, statistician)
  - Patrice Verpillat (EMA, epidemiologist)
  - Daniel Morales (EMA)
  - Olga Kholmanskikh (FAMHP, clinical/oncology)
  - Carla Torre (Infarmed, pharmacoepidemiologist)
  - Wolfgang Jaquet (FAGG-AFMPS, statistician)

How are we working on the RP?

- Concept paper was agreed by MWP and adopted by CHMP PROM and released for public consultation

  ...and today we want to hear from the stakeholders

- In 2026, we develop the concept paper to a reflection paper

1 24 July 2025
2 EMA/CHMP/225255/2025
3 Committee for Medicinal Products for Human Use (CHMP)/Methodology Working Party (MWP)

4 Draft Concept Paper on the Development of a Reflection
5 Paper on the Use of External Controls for Evidence
6 Generation in Regulatory Decision-Making
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Agreed by Methodology Working Party (MWP)	May 2025
To be adopted by CHMP PROM for release for consultation	14 July 2025
Start of public consultation	25 July 2025
End of consultation (deadline for comments)	31 October 2025

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Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support .

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Keywords	Clinical trial design, external controls, regulatory decision-making

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Starting point

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 randomized arm in that same protocol.

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.

What is planned to be discussed?

- Definition of an external control
- The appropriate clinical and regulatory setting and minimal requirements for external controls
- Operational and feasibility aspects
- Planning, design, conduct, analysis and reporting of studies for which external controls are used and related methodological aspects such as considerations on minimization of bias and confounding, the definition of estimands, target trial emulation, type 1 error control, sample size
- 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

What is not planned to be discussed?

- Use of historical data for contextualisation
- External control data used to augment randomised controlled trials
- Indirect comparisons using a network meta-analysis

Kiitos

Elina Asikanius

Elina.Asikanius@fimea.fi

www.fimea.fi