Regulatory Townhall: Regulatory Hot Topics

David Wright, Helle Lynggaard & Florian Lasch
Rima Izem, Elina Asikanius & Khadija Rantell

"We are a community dedicated to leading and promoting the use of statistics within the healthcare industry for the benefit of patients."

Regulatory Townhall

Non-inferiority and equivalence comparisons in clinical trials
Chair: David Wright, AstraZeneca

- *Florian Lasch, EMA*
- *Helle Lynggaard, Novo Nordisk*

Use of external controls and real-world evidence to support regulatory decision making *Chair: Rima Izem, Novartis*

- *Elina Asikanius, FIMEA*
- *Khadija Rantell, MHRA*

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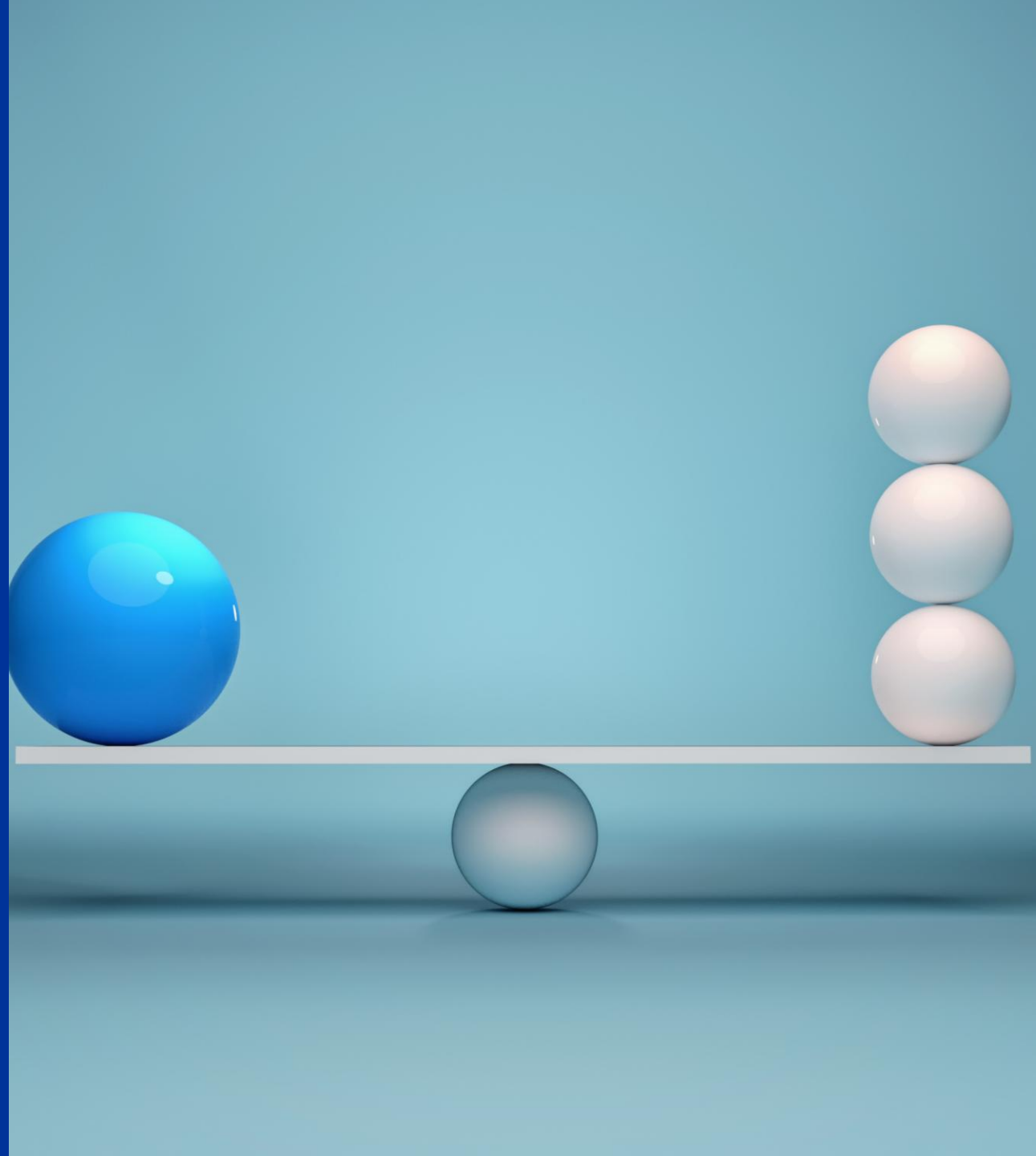
Draft guideline on non-inferiority and equivalence comparisons in clinical trials

Key recommendations

June 2026

Susanne Urach, Jonathan Bergman, Florian Lasch



Background

- **Draft** updated guideline published in October 2025

- The guideline replaces

  - the 'Guideline on the choice of the non-inferiority margin' (EMEA/CPMP/EWP/2158/99) and

  - The 'Points to consider on switching between superiority and non-inferiority' (CPMP/EWP/482/99)

- The public consultation closed on the 31st of May 2026 - comments **not** yet assessed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1 24 October 2025
2 EMA/301654/2025
3 Committee for Medicinal Products for Human Use (CHMP)/
4 Methodology Working Party (MWP)

5 Guideline on non-inferiority and equivalence comparisons
6 in clinical trials
7 Draft

Summary of key recommendations 1/3

- Applying the guideline requires multidisciplinary expertise
- Clear objectives:
  - absolute efficacy
  - relative efficacy
  - equivalence
  - non-inferiority safety
- Aligned methodological approach
  - objective – estimand – design – analysis
  - no **default** "ITT and PP analyses" – instead: sufficiently conservative main analysis

Summary of key recommendations 2/3

- Stronger role of pre-specification and impact assessments in the protocol and CSR
  - **Assay sensitivity**
  - **Constancy assumption:** Differences to historic trials – impact of expected differences? impact of observed differences?
  - **Estimands:** Intercurrent events – expected + observed patterns and frequencies
  - **Analysis**: Expected performance of new treatment compared to the active comparator, expected adequacy of estimator under different scenarios
- For absolute efficacy, we require an effect estimate of the new treatment against placebo

Summary of key recommendations 3/3

- Synthesis approach with safeguard tentatively accepted for demonstrating absolute efficacy

- Switching from non-inferiority to superiority requires pre-specified strategy for controlling the type-I-error

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Any questions?

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Follow us

Industry perspectives on EMA draft guideline on non-inferiority and equivalence comparisons in clinical trials

Helle Lynggaard, Novo Nordisk

17 June 2026

Disclaimer

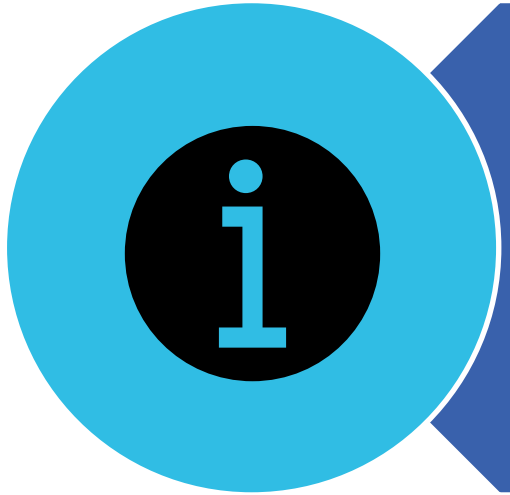
The views expressed in this presentation are not necessarily the views and practices of my employer.

Acknowledgements

- Members from Estimand Implementation Working Group (EIWG) sub-team on estimands in non-inferiority trials (www.eiwg.info)
  - Vivian Lanius (UCB)
  - Sue McKendrick (PPD, Thermo Fisher)
  - Franco Mendolia (Bayer)
  - Marian Mitroiu (Biogen)
  - Tobias Mütze (Novartis)
  - Sunita Rehal (GSK)
  - David Wright (AstraZeneca)
- Regulatory ESIG, especially Florian Voss (Sanofi)
- Everyone who sent their comments to the Regulatory ESIG (~115 comments)
- Thanks to EMA and the drafting group for the invitation to review

Agenda

New and valuable additions



Areas where more clarity would be helpful

New and valuable additions

New and valuable additions

- Objectives must be explicit and detailed
- Estimand framework is central
  - Importance of it in relation to **assay sensitivity and choice of margin** is emphasised
  - No expectation to default defining **two co-primary estimands**
- Role of per-protocol analysis set de-emphasised
  - Per-protocol analysis set plays no longer a role in the primary and secondary analyses

New and valuable additions

- Definition of “conservative”
  - Applies to the estimator and **not** to the estimand
- Guidance provided if constancy assumption is violated
- Justification and documentation requirements for assay sensitivity and margin strengthened
  - Requires clear rationale and evidence

Areas where more clarity would be helpful

Issue 1: Guideline too technical

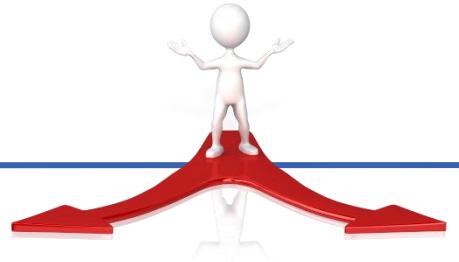
Key challenges

- Guideline targets statisticians, but it has **significant implications for clinicians and medical writers**
- Key areas requiring cross-functional input
  - Use of historical evidence
  - Assay sensitivity
  - Margin justification

Proposed change

- Include **clear, non-technical explanations** (layman's language) in key sections to support wider stakeholders

Issue 2: Absolute vs. relative efficacy



Key challenges

- Unclear **decision framework** for use of absolute and relative efficacy, including their role in
  - Regulatory conclusions
  - Benefit-risk evaluation
- Unclear if absolute efficacy **always** should be **confirmed** before evaluating relative efficacy

Proposed change

- Clarification of **roles** of the two objectives
- Acknowledge explicitly that absolute efficacy **cannot always** be evaluated

Issue 2: Example for when absolute efficacy cannot be established

Key challenges

- New insulin for patients with type 1 diabetes
  - Placebo is not an option
  - Individual dosing
  - Forced-titration according to glucose ranges
  - By design, **superiority cannot be demonstrated** versus another insulin
  - No historical placebo-controlled trials are available

Proposed change

- Acknowledge that absolute efficacy cannot always be evaluated and that in those situations, **relative efficacy is sufficient**

Issue 3: Constancy lacks operational clarity

Key challenges

- Focuses on **magnitude of effect only**
- Implicitly requires similarity in various aspects, e.g.,
  - Estimand
  - Trial population
  - Trial design and conduct
  - Endpoint assessment
  - Background medication/standard of care

Proposed change

- Clarify **how to operationalise** assessment of constancy assumption by clarifying which factors must be comparable

"Constancy assumption: the assumption that **the effect** of the active control in the non-inferiority or equivalence trial **is similar** to **the effect** in the past studies used for deriving the margin."

Issue 4: Increased documentation requirements are important, but may be challenging to implement

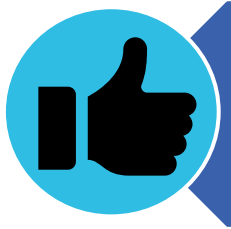
Key challenges

- Assay sensitivity and margin (protocol and report)
  - Required information (e.g., estimand from historical trials) **often not available and cannot be reconstructed**

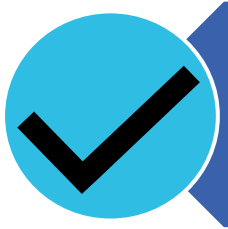
Proposed change

- Explicit recognition that information often is **unavailable**
- Clear guidance on what to do when **evidence is incomplete**

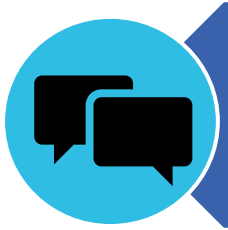
Summary



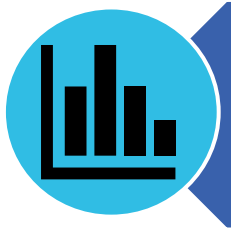
Overall: valuable and well-developed guideline



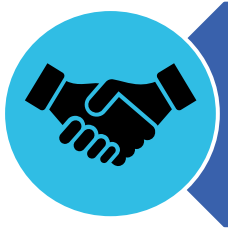
Important and timely update. Strong step forward, particularly in implementation of estimands



Clarity needed in key areas, including guidance on what to do in case required information is not available



Guideline would benefit from broader accessibility – include clear explanations for non-statisticians



Overall ask: Provide practical, operational guidance to support consistent implementation

Want to continue the discussions?

- We shall continue discussions at the EFSPI Regulatory Statistics Workshop, 19-20 August 2026 (Basel and virtual)

- www.efspiworkshop.org

Use of External Data Regulatory Townhall

Rima Izem,
rima.izem@novartis.com

PSI regulatory townhall /External control discussion

June 17th 2026

Acknowledging contributions of panelists and multiple (EFSPI/PSI SIG): RWD, small population, regulatory

External data – scope

- **External** to the clinical trial, the latter being the main source of evidence in regulatory settings

- **Data** from real-world data (RWD) sources, historical trials, natural history studies, … etc.

First comes **purpose**

- Purpose: fill a knowledge gap in the regulatory submission, including but not limited to primary evidence of efficacy

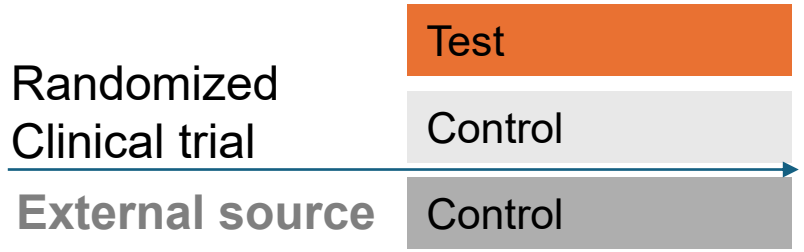
- Fit-for-purpose data : **relevant** and **reliable** data to the stated purpose

- Fit-for-purpose methods : **evidence synthesis** methods (e.g., causal inference, Bayesian dynamic borrowing)

Purpose, strategy, and study design

Compare Test to Control (efficacy or safety)

Gain efficiency/power for comparison of Test to Control



Compare Test to Control 2

Compare Test to Control for a long-term outcome and/or new population

Fimea
Lääkealan turvallisuus- ja kehittämiskeskus

EMA Reflection paper on External Controls

Elina Asikanius

PSI Conference June 2026

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 May 2026
EMA/125200/2026
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

Agreed by Methodology Working Party (MWP)	May 2026
Adopted by CHMP	21 May 2026

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

https://www.ema.europa.eu/en/documents/scientific-guideline/concept-paper-development-reflection-paper-use-external-controls-evidence-generation-regulatory-decision-making_en.pdf

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

Scope of the Reflection Paper

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.

- 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

What is planned to be discussed?

- 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

Kiitos.

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Medicines & Healthcare products Regulatory Agency

Use of external control arms based on real-world data to support regulatory decisions

MHRA draft guideline

Khadija Rerhou Rantell
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PSI conference, Belfast June 2026

Scope of guidance

In Scope

- **RWD ECAs** in clinical trials for regulatory submission
- Design and analysis considerations for RWD ECAs
- Use of RWD ECA as sole or augmenting control
- Protocol, bias, and justification principles
- Patient/public involvement
- Examples/scenarios for RWD ECA use

Not in Scope

- Use of **clinical study data as ECA**
- Specific statistical methods for RWD ECAs
- **Specific RWD sources**
- RCTs/observational studies mainly using RWD
- Natural history studies
- Disease/product-specific requirements
- Synthetic/virtual/in silico control arms
- Aggregate-level external controls
- Preferences for ECA source selection

Emerging themes based on feedback from public consultation

- Patient involvement and patient voice
- Methodological scope and non-prescriptive approach
- Hierarchy of evidence and use of ECAs
- Historical controls and timing
- Pre-specification, SAPs and amendments
- Addressing bias and statistical considerations
- Endpoints, data access and regulatory oversight
- Out-of-scope comments and future guidance
- Definitions and international alignment
- Examples, scenarios and scientific advice

Acknowledgements

Dr Rebecca Ghosh (MHRA)
David Brown (MHRA)
Maria Peppa (MHRA)

Copyright information

Discussion

References: guidelines and case studies related to external data/evidence

- ICH – E10 (2000), choice of control group in clinical trials
- US FDA (2018-2024) Many RWD/RWE guidelines and case studies
- European Medicines Agency (EMA)/Medicines and Healthcare products Regulatory Agency (MHRA) guidelines and case studies
  - (EMA, 2025b) Workshop on the use of external controls for evidence generation in regulatory decision-making
  - (EMA, 2025a) Workshop on the use of Bayesian statistics in clinical development
  - (MHRA, 2025) Draft guideline on the use of external control arms based on real-world data to support regulatory decisions
  - (EMA, 2024b) Reflection paper on establishing efficacy based on single arm trials
  - (EMA, 2024a) Reflection paper on use of real-world data in non-interventional studies to generate real-world evidence - Scientific guideline

- International guidelines in progress: ICH-E23, ICH-E24

Discussion

1. Per current guidelines, is any control data obtained from an RCT, even if small/short term, better than no control data + “robust” external controls?

2. Where do considerations for hybrid control design fit in your guidance development plans (current and upcoming documents)?

3. What does pre-specification mean when we use external data? How can pre-specification be documented? (e.g., within protocol and/or analysis plan of the clinical trial, or in standalone documents)?

Thank you

Back-up

Reflections from Peter Arlett (EMA) after the EMA workshop on external controls in November 3rd 2025 on the need for “deep knowledge of both clinical trial design and observational research”

Peter Arlett · 2nd
Head of Data Analytics and Methods...
9h ·

Connect

Running and reflecting: we need more experts able to bridge between clinical trials and observational studies

Weekends are for running and reflecting.

In recent weeks I have attended workshops on clinical trials and on observational studies. What was striking is how these communities of experts are largely separate. Even at an EMA workshop last week on external controls for clinical trials, which in many cases means using cohorts from electronic healthcare records or registries, many of those attending appeared to come from one camp or the other.

But if we’re going to advise on generating excellent clinical evidence and if we’re going to interpret evidence from across the spectrum of methods, we need our experts to have a deep knowledge of both clinical trial design and of observational research. So my call is for the next cohort of experts to be trained in both fields to be able to give that expert advice on design and interpretation that bridges from clinical trials to observational studies.

What do you think?