BIA consultation response

July 2025

BIA response to consultation on MHRA draft guideline on the use of external control arms based on real-world data to support regulatory decisions

Background

The MHRA has published a draft guideline on the use of external control arms (ECAs) based on real-world data (RWD) to support regulatory decisions. The consultation on the draft guideline closed on 14 July 2025.

The BIA's response to this consultation has been developed with input from members of the BIA's Regulatory Affairs Advisory Committee (RAAC).

Consultation questions

Overall comments

Please provide any general comments you may have on the draft guidance.

We welcome the MHRA's initiative in developing draft guidance on the use of real-world data (RWD) in external control arms (ECAs). The draft guidance signals a pragmatic approach to accepting RWD ECAs in situations where a fully powered randomised controlled trial (RCT) is impractical or unethical. The draft balances patient safety and methodological rigour with an openness to innovative evidence generation.

Please see below some points for consideration and suggestions on how the guidance could be improved.

- We welcome the flexibility exhibited by the statement "there is no general scenario where the use of RWD external controls is explicitly ruled out." However, it would be helpful for the guidance to provide additional examples of scenarios where RWD ECAs would be accepted, including in rare diseases, oncology and common diseases. The inclusion of quantitative benchmarks, such as effect-size thresholds, balance diagnostics or sample propensity-score reports, would also help to allow sponsors to evaluate, in advance, whether an ECA is likely to satisfy regulatory expectations.

- The guideline provides flexibility regarding the choice of statistical methodology, which is appreciated but in contrast with other regulatory agencies, such as FDA and EMA that have published more detailed guidelines, including examples of acceptable adjustment methods (e.g., propensity scores, inverse probability weighting) and bias mitigation strategies. It would be helpful for MHRA to provide similar examples or best practices to help sponsors better plan and document ECA approaches in line with regulatory needs.
- The guideline rightly emphasises the importance of data quality, but it does not provide a clear or operational framework for how data quality should be measured. The accompanying “MHRA guidance on the use of real-world data in clinical studies to support regulatory decisions” outlines relevant attributes such as accuracy, reliability, and provenance, but remains largely qualitative and descriptive and is not specific to the use of RWD in ECAs. Without quantitative metrics or structured methodologies to assess these dimensions, sponsors are left without a consistent basis for evaluating or demonstrating the fitness of RWD sources for regulatory use. Enhancing the guideline with greater detail on methodological considerations and data quality expectations – while preserving flexibility – would enhance clarity and support more robust, reproducible study designs, while ensuring alignment with international standards.
- While methodological rigor and transparency are essential in creating a robust RWD ECA, equally critical is close, iterative engagement to understand the "quality and fitness" of the data source, the rationale for its selection. Insights into data source feasibility, trade-offs and limitations, and their potential impact, is important in contextualizing approaches to minimize bias in the trial design, analysis and interpretation.
- In order to support regulatory alignment, the MHRA could reference relevant EMA or FDA guidance on the use of RWD and registries. This would support sponsors designing cross-jurisdictional studies and promote harmonisation across regulatory frameworks. The MHRA should also engage closely with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) on the drafting of a new efficacy guideline that proposes a systematic approach to using RWE in regulatory decision making.
- The MHRA should ensure that the language throughout the guideline is broad enough to accommodate the full range of data sources that could provide external controls,

including primary-use RWD, such as prospective registry studies designed to run concurrently with the externally controlled trial.

- It should be clarified if the guidance is suitable for supporting label extension or post-marketing studies. Randomisation is often impractical in these cases due to long follow-up periods leading to high dropout rates over the trial duration. The guidance may benefit from being split between trials that have ECAs as part of the trial design, and those incorporating ECAs once the trial has finished.
- It is unclear whether RWD used as an ECA could, in the appropriate settings, be included in the product label, particularly in support of efficacy claims.
- It would be helpful to specifically call out the Early Access to Medicines (EAMS) scheme in the guidance as it is an established opportunity to collect RWD.
- It would be useful to provide links to established sources of meta data e.g. HMA-EMA RWD catalogues, as studies using RWD are unlikely to be conducted in UK only.
- As MHRA and NICE are increasingly working closely together, including plans for integrated scientific advice and parallel assessment processes, it is necessary to establish if this guidance is aligned to what would be expected for HTA assessment.
- Replacing or reducing an internal control arm can decrease site numbers, monitoring expense and enrolment time. Those savings are partially offset by licensing fees for high-quality RWD, data-quality audits and advanced analytics. A concise annex illustrating typical cost trade-offs would help sponsors and HTA bodies budget more accurately.
- We recommend publishing the guideline as a living document, updated on a defined schedule to reflect evolving data-quality standards and methodological advances.

Overview

Please provide any general comments you may have on the draft guidance in this section.

- MHRA encourages sponsors to engage with them via scientific advice to discuss use of RWD. It would be helpful to clarify other routes available for discussion, such as through the Innovative Licensing and Access Pathway (ILAP).

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UK BioIndustry Association

Scope

Please provide any general comments you may have on the draft guidance in this section.

N/A

General principles and regulatory acceptability of designs depending on external real-world data controls

Please provide any general comments you may have on the draft guidance in this section.

- The guidance should provide examples of "situations where conducting an adequately powered randomised trial is not ethical or feasible, would result in a significant delay, or where the effect of the intervention is expected to be large enough to allow interpretation of the study results despite potential bias".
- It would be helpful to understand where ECAs could be utilised in more common diseases where adequately powered randomised-controlled trials take several years to complete, potentially causing significant delays to patient access cost-effective new treatments. We acknowledge that applying a single-arm study design to common diseases poses challenges. Nonetheless, employing a hybrid control approach – combining randomised internal control with external control – could enhance traditional RCTs and improve drug development efficiency for these common diseases. Additional guidance on this topic would be highly beneficial.

Types of studies and points to consider

Please provide any general comments you may have on the draft guidance in this section.

- The emphasis on "fitness for purpose" is appropriate and further, a tiered accreditation scheme for UK data sources would accelerate feasibility assessments and reduce negotiation time between sponsors and reviewers.

- The guidance would benefit from clearer protocol requirements for studies using ECA. While the Statistical Analysis Plan (SAP) for a single-arm trial must refer to external data to produce efficacy estimates, experience with the FDA and EMA is that a separate Non-Interventional Study protocol for the RWD study that forms the ECA is required.
- The guidance provides limited discussion on the importance of conducting sensitivity analyses and quantifying the potential magnitude of unmeasured or residual confounding. While there is a brief mention of this topic in lines 306–308, it would be beneficial to place greater emphasis on the importance of quantifying unmeasured or residual confounding, and highlighting methodologies to assess unmeasured confounding.
- The guidance should cover the use of data from academic or healthcare databases for RWD purposes in a MAA if the owner of the database is not prepared to give full access to the sponsor to respond to MHRA questions during the MAA procedure.
- In the section on 'Using RWD to augment a randomised internal control arm', it would be helpful to provide further guidance on the methodology for combining the ECA data and the randomised arm, as well as examples of what not to do.
- It could enhance clarity to reorganise paragraphs 30–52 into key categories such as Data Sources, Study Design, Study Populations, Exposures, Endpoints, Covariates, and Analyses would enhance clarity, with bias considerations being a thread throughout all these aspects.
- The guidance should consider potential bias due to irregular and less frequent efficacy assessment in RWD.
- In matched cohort analyses, there can be issues in defining "time zero" of observational cases compared to trial data and patients may be eligible at different timepoints. In studies where overall survival is the primary endpoint, it would be helpful to understand the MHRA's view on using target trial-emulation approaches to reduce the risk of overall survival being artificially diminished.
- The guidance could specify advised methods to reduce the risk of confounding, including if machine-learning methods are encouraged.

- It would be helpful to provide examples of acceptable and non-acceptable data imputation methods.
- The guidance could mention ensuring confidentiality of patients providing RWD.
- The principles outlined for RWD ECAs may also apply to external controls derived from other sources, such as completed clinical trials. It is not clear in the guidance how points to consider regarding RWD would also apply to completed clinical trials data.

Example of scenarios, endpoints and designs

Please provide any general comments you may have on the draft guidance in this section.

- The rare disease example scenario provided here is welcome. As set out in previous comments, additional examples in other disease areas would be helpful.

Advice

Please provide any general comments you may have on the draft guidance in this section.

N/A

About the BIA

The BIA is the trade association for innovative life sciences and biotech industry in the UK, counting over 600 companies including start-ups, biotechnology, universities, research centres, investors and lawyers among its members. Our mission is to be the voice of the industry, enabling and connecting the UK ecosystem so that businesses can start, grow and deliver world-changing innovation. For any further information regarding to this consultation response, please contact Rosie Lindup, Senior Policy and Public Affairs Manager, at rlindup@bioindustry.org.