CRDSA

Clinical Research Data Sharing Alliance

External Controls

MHRA, EMA, and FDA Evolving Regulatory Approaches

20 October 2025

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1.Introduction

Clinical trial design continues to evolve at a remarkable pace, driven by advances in data science, regulatory shifts, and a growing focus on patient-centricity. Against this backdrop, the definition and role of "external controls" has become increasingly relevant for evidence generation to support regulatory decision-making. Sponsors are seeking greater regulatory clarity in how external controls can be judiciously utilized to both safeguard scientific rigor and address pressing challenges in clinical research.

Recent draft documents by regulatory agencies reflect this dynamic environment. In May 2025, the UK Medicines and Healthcare products Regulatory Agency ("MHRA") published a "draft guideline on the use of external control arms based on real-world data to support regulatory decisions". [1] In late July, the European Medicines Agency ("EMA") published for public comment a "Draft Concept Paper on the Development of a Reflection Paper on the Use of External Controls for Evidence Generation in Regulatory Decision-Making". [2]

Along with the U.S. FDA's 2023 draft guideline on the design and conduct of externally controlled trials[3], these documents aim to define the boundaries of external control usage. However, notable differences exist in how these agencies conceptualize external controls.

This whitepaper summarizes the scope and strengths of the MHRA draft guideline, contrasting it with the FDA draft guidance and EMA's proposed scope for the reflection paper. We also address areas where further methodological clarity is needed to support sponsors and regulators in the regulatory use of externally controlled clinical trials.

2. External Controls: Definition and Scope

The MHRA draft guideline scope includes both single-arm (active drug) studies (fully externally controlled) and augmented control arms, in which a randomized comparator arm is supplemented with external data. The term "supplemental" is also commonly used to describe the latter type of trial design.[4][5] Another term that may be used is "hybrid" although this may also refer to non-concurrent controls using more than one type of data (e.g., prior trial and real-world data).

In contrast, the FDA draft guidance uses "external" to denote only trials where there is no concurrent control and, likewise, the EMA development scope is limited to 100% replacement of the concurrent control with externally sourced data, with augmented trial designs specifically out of scope.

It is significant that MHRA has adopted a broader definition inclusive of all trial designs where an external control is employed. This addresses one of the gaps in the FDA draft guideline (and EMA's proposed reflection paper scope), as highlighted in CRDSA's 2023 submitted comments to FDA :

> "One approach is to consider external control designs as a subset of supplemental controls, occurring in specific instances where a single-arm trial design is warranted.
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> While implementing supplemental control designs may differ from external controls, the specific considerations around data source and suitability are more a matter of degree than substantively differing design characteristics. As such, we recommend expanding the guidance scope to include constructing a supplemental control where a concurrent control is present. Further, sponsors would benefit from clarity around the FDA's approach to risk assessment of different control types. Finally, for clarity and to avoid conflicting interpretations, we recommend the development of a single guidance inclusive of supplemental and external trial designs." [6]

In fact, the MHRA draft guideline states explicitly that "A randomised trial with an internal control arm which is augmented with external controls is preferred to a single arm trial with only an external control, as such a design allows for better control of potential biases."

The MHRA's broader definition of external controls is more than a semantic distinction—it positions the agency to accommodate a wider range of innovative trial designs without sacrificing scientific rigor. By explicitly valuing augmented designs that blend internal and external arms, MHRA acknowledges the reality that ethical, logistical, and feasibility constraints often demand flexibility. This stance not only bridges a critical gap left by the FDA's narrower approach (and potentially that of EMA) but also creates an opening for trial strategies that can enhance diversity, improve patient experience, and reduce unnecessary exposure to control arms. Importantly, supplemental trial designs can allow for adaptative execution, should the performance of the concurrent control arm differ from the external control. In these cases, the internal concurrent control arm could be strengthened by increasing enrollment, with the external control influence reduced, or abolished. Conversely, if the performance of the concurrent and non-concurrent control is closely matched, it may be feasible to transfer patients from the internal control to the investigative arm, thereby enhancing the evidence generated from the investigational arm.

As noted by EMA "…a standard definition of external controls is currently not available." We think that the MHRA's stated preference represents a more rational and flexible approach to trial design, recognizing that the trial design does not need to be a binary choice between fully external (no concurrent control) and a traditional RCT [5]. We encourage EMA, FDA, and other regulatory bodies to adopt this broader definition of "external control," allowing for more flexible trial designs that include both concurrent and non-concurrent control arms.

3. Types of Data

While the MHRA draft guideline primarily focuses on the use of RWD, it acknowledges the relevance of its core principles to other data types such as prior Clinical Trial Data ("pCTD"). The guideline encourages engagement and proposals for utilizing various data sources, recognizing the broader applicability of its foundational concepts. This inclusive approach suggests a move toward a more comprehensive framework for regulatory submissions. Notably, EMA's draft concept paper introduction does reference data derived from other clinical trials, real-world data or other data sources (although this is not explicitly stated in the proposed reflection paper scope).

CRDSA 2024 publication, "Data Reuse in Regulatory Submissions: The Role of Data Platforms" [7] delves into the similarities and distinctions between the processing and sharing of RWD and prior trial data. The document proposes key principles applicable to both data types, addressing crucial aspects such as data collection, data documentation, and quality assurance, including regulatory audits.

CRDSA recommends that, where possible, regulatory agencies consider prior trial and real-world data together, accounting for differences within a cohesive and consistent framework.

4. Regulatory Mindset

The MHRA draft guideline exhibits a more favorable stance towards the utilization of external controls when contrasted with the FDA draft guidance. This positive perspective is highlighted by the inclusion of use case scenarios where the recruitment for a conventional randomized controlled trial (RCT) would result in significant delays, potentially hindering timely access to beneficial treatments.

Furthermore, the MHRA draft suggests a pragmatic approach, indicating that a positive regulatory decision can be reached if the data is sufficiently convincing, despite the availability of alternative approaches that may have been ideally preferred. This emphasis on the strength of the evidence, rather than strict adherence to traditional methodologies, signals a willingness to adapt to real-world challenges and accelerate the appropriate evaluation of promising therapies, while maintaining scientific rigor.

The MHRA's willingness to embrace more innovative, hybrid approaches stand in contrast to the FDA's narrower use scope. Because running multiple programs for different regions is impractical, we strongly encourage FDA and EMA to emulate MHRA and take a similarly expansive and forward-thinking approach, supporting global drug development strategies that work across regions and regulatory authorities.

5. Methods and Statistical Approaches

Recognizing that methods and statistical approaches are outside the immediate scope of the MHRA draft guideline, both sponsors and regulators still share a strong need for a clear and consistent framework when it comes to designing and evaluating externally controlled trials. Without such guidance, variability in practice can undermine the credibility and comparability of study results. A well-defined set of best practices will promote transparency and enhance the evaluation of new therapies, enabling regulators to more quickly dismiss ineffective therapies and speed the delivery of effective treatments to patients.

We applaud EMA for including both "operational and feasibility aspects" and "planning design, conduct, analysis and reporting of studies for which external controls are used and related methodological aspects…" in the proposed reflection paper scope. These are critical areas that must be addressed to ensure trial design and execution will address regulatory concerns.

To support such efforts to establish guidelines and best practices, CRDSA has designed an External Controls Demonstration Project. This initiative aims to develop and refine methodologies that support the regulatory use of both prior clinical trial data ("pCTD") and RWD. Central to the project's objectives is the creation of recommendations that ensure cohort development is reproducible, while minimizing variability and guarding against bias that could arise from selectively favorable data. The project also examines trial design considerations, including exploring methods for determining appropriate proportions of replacement—such as 10%, 25%, or 50%—in augmented trials, assessing statistical power and confidence interval coverage for non-concurrent control arms, and conducting performance evaluations of different cohort development methodologies.

6. Conclusion

For many use cases, patients are best served by a regulatory approach that considers the totality of available evidence, including all available and relevant external data sources. The MHRA draft guideline recognises the range of potential external control use cases and design approaches, representing an important step towards advancing the responsible use of diverse data sources in regulatory approvals.

Looking ahead, continued collaboration among sponsors, regulators, patient groups, and organizations like CRDSA will be essential to refine best practices and ensure robust, reproducible cohort development. The ongoing work to establish clear standards for externally controlled trials, including rigorous assessment of statistical and methodological foundations, promises to enhance the credibility and comparability of regulatory decisions.

It is crucial for regulatory authorities to recognize that, in the vast majority of trials, the patients are from diverse regions and jurisdictions. Since applications for regulatory approval are broadly based on the same evidence, consistency amongst regulators is critical. Without regulatory harmonization, sponsors are left to reconcile contrasting, and sometimes conflicting, guidance ultimately slowing the drug development process and leading to potentially substantial delays in delivering needed therapies to the patients being served.

7. References

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