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Clinical Research Data Sharing Alliance

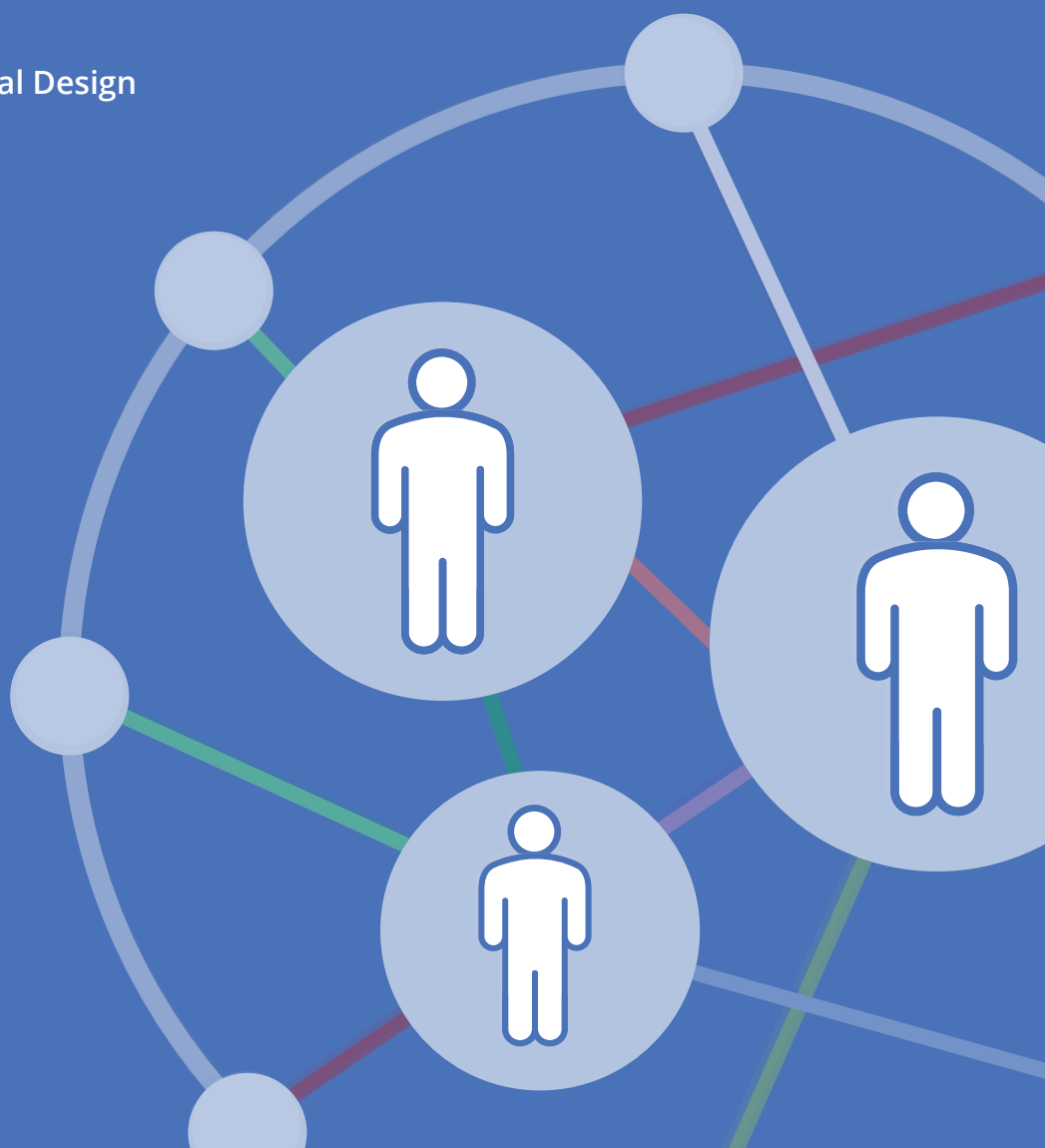
FDA Draft External Controls Guidance: Situation Analysis and Recommendations

Work Group: Innovative Trial Design

Date: 21 August 2023



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Introduction

On January 31, 2023, the U.S. Food and Drug Administration released a draft guidance on externally controlled trials for public comment.¹ The comment period closed on May 2, 2023, with over 200 responses from industry sponsors, patient advocacy organizations, academic research institutions, nonprofit consortia, and patients.

Commenting organizations commended the FDA for developing the draft and acknowledged the effort and diligence needed to begin to address this complex area. The public comments also highlighted a range of substantive considerations.²

The draft guidance and public comments, taken together, present a clear picture of the challenges to address. On July 19, 2023, the Clinical Research Data Sharing Alliance (CRDSA) hosted a virtual roundtable to discuss the issues raised by commenting organizations and explore ways to ensure the expanded use of alternative control designs in regulatory submissions. The webinar slides and recording can be accessed in the [resources section](#) of CRDSA's website.

Over an engaging two hours, a panel of experts representing 12 organizations ([see next page](#)) held a wide-ranging dialogue with two primary objectives:

1. Identify key regulatory barriers to adopting trials using external and supplemental/hybrid control designs.
2. Determine collaborative actions to address those barriers, supporting FDA and other regulatory agencies to ensure a regulatory environment that supports alternative control trial designs.

The roundtable agenda was informed by a review of over 60 submitted organizational comments, an in-depth analysis of 31 comment documents, and a pre-meeting registrant survey.

While acknowledging the enormous task of developing the draft guidance, and its rigor within a limited scope, the panelists spoke with both urgency and concern over perceived problem areas and offered recommendations on how to advance and broaden the discussion. They systematically looked at what this community can do to help FDA address both the challenges and opportunities inherent in using these designs.

This report summarizes discussion highlights, outlines key regulatory challenges, and includes recommended actions developed by consensus subsequent to the roundtable. We invite and encourage additional community involvement and input on the recommendations.



Roundtable Panel

American Society of Clinical Oncology, CancerLinQ (ASCO CancerLinQ)

Robert Miller, Chief Medical Science Officer

Association of Clinical Research Organizations (ACRO)

Ruthie Davi, Senior Vice President, Data Science, Medidata

Clinical Research Data Sharing Alliance (CRDSA)

Peter Mesenbrink, Executive Director of Biostatistics, Novartis, and CRDSA Board Chair
Aaron Mann (Moderator), Chief Executive Officer

COTA Healthcare

Laura Fernandes, Senior Statistical Director

Critical Path Institute (C-Path)

Shu Chin Ma, Vice President, Model-Informed Drug Development and Quantitative Medicine
Jagdeep Podichetty, Senior Director of Predictive Analytics, Quantitative Medicine Program

Cystic Fibrosis Foundation

Natanya Kerper, Policy Manager, Research and Development

Duke Clinical Research Institute | Duke University Medical Center

Frank Rockhold, Professor of Biostatistics and Bioinformatics and CRDSA Board Director

Duke-Margolis Center for Health Policy

Rachele Hendricks-Sturup, Research Director, Real-World Evidence

Muscular Dystrophy Association

Paul Melmeyer, Vice President, Public Policy and Advocacy

Project Data Sphere

Jon McDunn, Executive Director and CRDSA Board Director

TransCelerate Biopharma, Inc.

Jessica Lim, Director, Statistics, GSK, and TransCelerate Clinical Data Sharing Leadership Team

UCB

Estelle Michael, RWE Engagement and Policy Lead



External Controls: Use Cases

Recording Timestamp: 11:30

The roundtable opened with the panel exploring key use cases for external controls. Rare diseases figured prominently in the discussion, and patient advocates spoke of the great potential that external controls would have in a context where often no treatment currently exists, where slow-progressing and heterogeneous diseases pose challenges to conventional practice, and where randomization to placebo may not be ethical or feasible.

However, the implications go beyond what has typically been considered rare disease. The panel discussed how the application of precision medicine changes patient recruitment and evidence-gathering. As one example, cancer can increasingly be seen as a collection of rarer diseases — as malignancies characterized by tumor cell biomarkers define increasingly targeted and narrow patient populations.

Several panelists mentioned the value of external comparator arms in overcoming recruitment challenges in the face of patient reluctance to go on placebo or standard of care, and in making trials faster and more efficient through such reuse. Building on the patient perspective, panelists noted that patients want and expect safe and responsible data reuse. They said that concerns about confounding and bias associated with external controls can be addressed through proper planning and that there are many statistical methods that can be employed to minimize associated biases. They suggested that the value of the data to the patient population outstrips the perceived risks, assuming responsible mitigation.



Key Regulatory Challenges

Recording Timestamp: 40:00

The introduction established the aim of understanding and aligning on core “gating” issues raised by the draft guidance. The selection of topics was informed by the analysis of organizational comments. The topics shared three general characteristics: relevance across all data types and sources (e.g., real-world data and historical clinical trial data); relevance across clinical trial types (i.e., generally not trial- or situation-specific); and mention in detail by multiple commenting organizations.

This section of the roundtable is divided into four topic areas:

- **Source data access**
- **Trust and provenance**
- **Guidance scope**
- **RCT benchmarking**

Because these topics were included in filed organizational comments, this report uses selected excerpts from those documents to illustrate each area. Roundtable recording timestamps are included for reference to the full panel discussion, and links to the public comment documents can be found in the [References section](#) below.

Source Data Access

Recording Timestamp: 41:30

Background

The first topic considered was regulatory access to source data. In the Considerations to Support Regulatory Review section, the draft guidance states (emphasis added), “Sponsors should also ensure that FDA has access to source documents and *source data for the external control arm* as part of an FDA inspection or upon request. The draft guidance glossary then defines source data and documents as “All information in original records and *certified copies of original records* of clinical findings, observations...” and “*Original documents, data, and records* (e.g., hospital records; clinical and office charts; laboratory notes....”

The importance of clarifying source data access requirements cannot be overstated. The issue was raised by almost two-thirds of organizations included in CRDSA’s detailed comments analysis.



Representative Comments

Defining source data in secondary use:

CRDSA: “An external control requires the secondary use of an original data source dataset collected for another purpose.... To be used for secondary research, the original datasets and documentation are processed for secondary use, most commonly to protect patient privacy. Therefore, at the point of secondary use, ‘source data’ is generally defined as data and documents accessed on a data-sharing platform, through an internal data repository, or otherwise constructed from data derived from original sources.”³

TransCelerate: “Given the requirements of the General Data Protection Regulation (GDPR) in Europe, and several similar regulatory requirements that have emerged in the years since the GDPR was instituted, many companies choose to anonymize clinical trial data. Once data is anonymized, it is no longer considered personal data, meaning it is not subject to GDPR or similar regulations. This approach benefits both sponsors and patients and has been widely adopted in data sharing. Much of the patient-level data contributed to data sharing consortia is anonymized data”⁴

Potential consequences if the final guidance retains the draft definition of source as original data and documents (emphasis added):

ASCO: “We suggest the final draft guidance define use of external controls in the context of secondary use, since the proposed language *could pose serious challenges to creation of an external control.*”⁵

Muscular Dystrophy Association: “Many of these studies include a prohibition on patient-level data leaving the natural history study, and *if it occurs, it would violate the informed consent* document signed by participants.”⁶

Duke-Margolis: “We appreciate the FDA’s recognition in the guidance that private parties will have to coordinate data access; although, the level of access the FDA is requesting could add trial burden that *might render external controls infeasible.*”⁷

ACRO: “ACRO therefore respectfully submits that a requirement to make available to FDA the actual ‘source documents’ and ‘source data’ of patients / participants of an external control arm presents as *unnecessary for compliance* with FDA regulations (21 CFR 314.50(f) and 601.2) and the policy goals underpinning those regulations, as well as *being detrimental to the creation and use of external control arms for marketing applications.*”⁸

CRDSA: “As written, the draft language and glossary definition of ‘source data’ would make it virtually impossible to construct an external control that meets regulatory standards, regardless of the use case or patient population need.”³

Trust and Provenance

Recording Timestamp: 1:07:50

Background

In the Design Considerations Overview, the draft guidance states, “Specific design elements to prespecify...include suitable study data sources.” Commenting organizations noted that “suitability” includes elements such as study and subject selection methodology, data integrity and verification, data completeness, and audit requirements (“traceability”).

The draft guidance invites sponsors to consult with FDA early in the development process to, among other things, discuss how proposed data sources are “fit for use.” Commenting organizations pointed out challenges with this “one-off” trial-specific approach and highlighted the need for the final guidance to address consistent standards for acceptable suitability.

Representative Comments

ASCO: “...it is important that the ‘suitability study data sources’ be clearly defined.... In addition, we recommend that the methods applied for data pre-processing (i.e., transforming source data to de-identify) be provided in detail to ensure that approaches are sound and yield data that are, in fact, suitable for analytic use.”⁵

C-Path: “...we suggest the agency clarify how data cleaning and formatting procedures, specific to the sponsor, might affect the overall quality and comparability of the resultant data.”⁹

COTA: “Rather, FDA should focus on the methodology by which the source data is abstracted and transformed to ensure adequate quality measures and constraints are in place.”¹⁰

CRDSA: “Data source suitability is foundational for other considerations, such as comparability, and may, in some cases, mitigate specific statistical and other bias concerns. However, absent clear best practice guidance on addressing those considerations, each sponsor is left to determine what constitutes appropriate source data suitability. This can result in two negative consequences. First, the sponsor cannot be sure that, at submission, the regulatory assessment of the data sources used will align with their determination. Second, the FDA (and other regulators) must align on ‘suitability’ sponsor-by-sponsor and trial-by-trial.”³



Guidance Scope

Recording Timestamp: 1:15:30

Background

The draft guidance introduction states, “Finally, this guidance also does not discuss considerations for using external control data to supplement a control arm in a traditional randomized controlled clinical trial.” Commenting organizations highlighted the importance of developing comprehensive guidance inclusive of a broader range of alternative control designs and/or ensuring that separate guidance documents are not in conflict with each other. In addition to fully external controls, areas put forward for consideration include supplemental controls (also referred to as hybrid controls), rare disease-specific guidance, summary-level data, and data derived from advanced analytic approaches (e.g., synthetic controls).

Representative Comments

Supplemental control designs:

ASCO: “...investigators and sponsors will benefit from clearly understanding FDA’s perspective on how implementation of supplemental controls might differ from external controls, FDA’s overall approach to risk assessment of differing control types, and data analytic approaches”⁵

COTA: “Based on the publications from the Agency (Mishra-Kalyani et al.) expounding the merits of implementing unequal randomization with a concurrent control supplemented with an external control, it was surprising to note that the guidance does not address the use of supplemental or hybrid controls.”¹⁰

CRDSA: “Unless the guidance is expanded to incorporate supplemental control development, there is a substantial risk that sponsors will consider this guidance as definitive for all controlled clinical trial designs.”³

Rare disease use cases:

ACRO: “The Draft Guidance makes no reference regarding specificities in the pediatric or extremely rare disease populations. These may be important to include as randomized studies may be difficult to execute for ethical reasons and so external control arms may play an important role. For life-limiting conditions, inclusion of data from other jurisdictions or historical sources may be required to act as the only viable reference group.”⁸

Muscular Dystrophy Association: “We disagree with FDA’s disregard of disease prevalence as still far too often we see treatment development efforts in ultra-rare neuromuscular diseases fail because FDA inflexibly layers approaches used in common or non-ultra-rare diseases onto ultra-rare diseases. FDA should never disregard the challenges unique to ultra-rare disease drug development.”⁶



Summary data:

Duke-Margolis: “Although the present draft guidance considers summary-level estimates out of scope, it would be helpful for the FDA to define and discuss, if possible, the potential regulatory value of summary-level estimates.”⁷

RCT Benchmarking

Recording Timestamp: 1:34:15

Background

The draft guidance provided a detailed perspective on design considerations for externally controlled trials, focusing on “important **confounding** factors and sources of **bias**” (emphasis theirs). The guidance also provided a table, Summary of Considerations for Assessing Comparability of Data, which detailed comparison focus areas (e.g., time periods, diagnosis, intercurrent events). Commenting organizations noted that traditional RCTs can also have sources of bias or unmeasured confounding factors (latent variables).

The panel discussed the provocative question of whether we can still assume the randomized controlled trial to be the gold standard for clinical research. There was general agreement that the RCT can represent a benchmark standard in very specific circumstances for well-designed and well-controlled trials with a large sample size. However, the definition of “well-controlled” will fall on a spectrum and, in some cases, a clinical trial, through design or execution, may not meet an “ideal” standard. The point was made that statistics can’t make every trial look like an ideal-state RCT — the concessions made in an external or supplemental trial design must be balanced against reasons for an alternative control. These include the clinical situation, inability to randomize, patient acceptance, and the scientific need.

Representative Comments

DIA-Innovation Design Scientific Working Group: “All of these additional factors mentioned in these lines [Summary of Considerations Table] are not unique to external control arms but applicable to all clinical data and not different to data collected for clinical trials. Randomization is unable to balance all these factors in small sized global trials; and these factors are also applicable to approvals based on single-arm trials.”¹¹



Cystic Fibrosis Foundation: “For such cases, we believe that it may be detrimental to discourage or set an unrealistic standard for the utilization of external control data from previously completed clinical trials when its use may be appropriate and justifiable. Furthermore, this position is at odds with the historical use of external controls in the FDA’s regulatory decision making; there are numerous examples of using external control data from previously completed clinical trials for regulatory purposes, including to support the approval of medical products.”¹²

COTA: “Lack of blinding is common practice in many oncology clinical trials and hence these concerns are applicable to such RCT trials too. Randomization does not take care of lack of blinding and there are no tools to account for this bias in RCTs and single arm trials.”¹⁰

Final Thoughts

Recording Timestamp: 1:48:00

The roundtable closed with panelists sharing their final thoughts. The panelists applauded the FDA for crafting the draft and expressed a strong desire to support the agency in further work on the guidance. A consistent theme was the need for collective action, including the involvement of regulators and patient advocacy groups, to develop and refine ideas supporting the use of alternative control trial designs. This can be achieved by convening future panels and workshops to build a framework of accepted processes and practices; developing approaches across the spectrum of evidence needed to answer clinical questions; and considering the data infrastructure needed to ensure trustworthy and acceptable evidence generation.



Recommendations

The draft guidance is an important step toward advancing innovative trial designs that are responsive to the needs of patients. It's also clear that diverse data sources and statistical methods present unique regulatory challenges.

In convening the July roundtable, CRDSA aimed to facilitate the development of a community of interest, including the 300-plus registered attendees and all organizations that contributed to the public comment period. The following recommendations are a starting point for collaborative actions this community can take to help ensure a global regulatory environment that supports the responsible use of diverse data types and sources in innovative clinical trials designed to advance science and serve patients.

Active regulatory engagement and continuous dialogue will be critical to ensuring that community-driven efforts meet health authority needs. While the focus of the roundtable, and this analysis, has been on the FDA guidance, it's also important to understand and address the needs of other regulatory agencies. As one example, in April, the European Medicines Agency published a draft paper on the evidence considerations from single-arm trials.¹³ Regulatory alignment on approaches will be critical as sponsors navigate the global clinical development environment.

Recommendation 1: CRDSA, in collaboration with interested organizations, will convene a series of topic-specific workshops to collect input from stakeholders and build toward consensus on key issues regarding use of external control data in clinical trial evidence generation.

Recognizing the complexity of the issues, we recommend convening a series of workshops to address specific challenges. These workshops may be virtual, in-person, or hybrid, with workshop outputs designed to support guidance development. Critical topics, in suggested order of priority, include:

1. Source data: Definition of "source" for secondary use and regulatory access.
2. Data trust and provenance: Developing guidelines for study and subject selection methodology, data integrity and verification, data completeness, and audit requirements ("traceability").
3. Guidance scope: Evaluation of alternative control trial designs, including supplemental controls, to determine common considerations and identify areas needing modifications or specific guidance development.
4. Terminology: Alignment on the application of key terms. Some definitions requested by commenting organizations included: externally controlled trials, external control arm, hybrid, synthetic, virtual, substitution, missing data (for RWD), and external comparator cohort.
5. Rare and ultra-rare diseases: Considerations for patient populations where it is not possible or practical to design trials with a concurrent control.
6. Clinical outcomes that require long-term follow-up: Although it may be possible to evaluate surrogate endpoints with a control arm, it is often challenging even in more common diseases where regulatory guidance requires demonstrating long-term effectiveness (e.g., non-alcoholic steatohepatitis).

Recommendation 2: Execute appropriate demonstration projects that provide insight into the implementation of proposed solutions and methodological approaches.

Demonstration projects will show how a proposed solution or approach looks in practice. There is ample precedent for using demonstration projects in guidance development — conducting demonstration projects was one of the four pillars of the FDA's Real-World Evidence Program development.¹⁴ Examples of current initiatives and ones proposed through the public comments include:

Supplemental controls demonstration project (CRDSA): This initiative creates a secure research repository of secondary non-small-cell lung cancer clinical trial and real-world data, allowing practical exploration of approaches, processes, and methodologies designed to support responsible secondary data use in regulatory pathways.³

Development of a cloud-based or data enclave platform to facilitate FDA access to patient-level RWD (Duke-Margolis, proposed): This project would explore a solution to provide FDA with access to the data without transferring possession and without compromising propriety or privacy. The agency could be provided with the necessary access and visibility to query, audit, and replicate analyses without the external control data leaving the owner's system.⁷

External control decision tool (Janssen, proposed): This project would develop an interactive decision tool to help sponsors identify when an externally controlled trial is an appropriate alternative. This would help sponsors step through questions regarding target population; prevalence; availability of comparator treatments at clinical equipoise; urgent unmet medical need; data source availability and validity for key outcomes (efficacy and safety) and clinical characterization; ethical considerations; and other questions that support or refute use of an external control arm (ECA) for a single-arm trial.¹⁵

In closing, we welcome additional suggestions or recommendations from the community. You can contact the CRDSA Innovative Trial Design work group at itd@members.crdسالiance.org.

About CRDSA

CRDSA is a multi-stakeholder alliance that serves the clinical data-sharing ecosystem. Our mission is to accelerate the discovery and delivery of life-saving and life-changing therapies to patients by expanding the research value of secondary use data. Broad access to these data has the power to transform the research process, improve trial design and delivery, and benefit the patients who donate their time and their data as part of the clinical development process. To find out more please visit crdsalliance.org.



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