

May 1, 2023

Lauren K. Roth
Associate Commissioner for Policy
Food and Drug Administration, Dockets Management Staff
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: ACRO comment submission
Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products [Docket No. FDA-2022-D-2983]

Dear Ms. Roth:

The Association of Clinical Research Organizations (ACRO) represents the world's leading clinical research and technology organizations. Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices, from pre-clinical, proof of concept and first-in-human studies through post-approval, pharmacovigilance and health data research. ACRO member companies manage or otherwise support the majority of all biopharmaceutical sponsored clinical investigations worldwide and advance clinical outsourcing to improve the quality, efficiency and safety of biomedical research.

ACRO thanks the Agency for releasing this draft guidance on *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products*. ACRO is pleased to provide the following feedback. ACRO would like to provide general comments, before moving on to specific lines within the guidance.

General comments:

The draft guidance focuses on the use of patient-level data from other clinical trials or from real-world data (RWD) sources, such as registries as well as electronic health records and medical claims. As the guidance notes, there are a number of areas not covered within the guidance, including other types of external controls, details of the design and analysis of a natural history study, nor the reliability and relevance of various sources of RWD that could be used in an externally controlled trial, nor considerations for using external control data to supplement a control arm in a traditional randomized controlled clinical trial. We appreciate that other guidance documents are in development and would suggest that it would therefore be helpful to include in this general summary a description of how all subsequent guidance documents interconnect.

The Draft Guidance covers many of the types of external control which have been published and the structure is to be welcomed. The recognition that different sources are relevant for different situations is also useful.

The Draft Guidance does not address retention periods for the data, records and reports generated in connection with a clinical study based on real world evidence that is used for equivalent regulatory purposes. In a conventional clinical trial conducted under Investigational New Drug (IND) authority, 21CFR312.57 requires that *“A sponsor shall retain the records and reports required by this part for 2 years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA has been so notified.”* ACRO asks for the final guidance to clarify that the retention period for RWE data is no longer than that required for records and reports of conventional clinical trials conducted under IND authority. Consequently, we recommend that FDA include expectations for retention consistent with those in 21 CFR § 312.57.

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. It would also be helpful to include comment regarding acceptable external control group approaches for extremely rare conditions where variability of treatment decisions may mean that electronic health records are not sufficient to act as controls.

Line-Specific Comments:

Lines 20-22

The Draft Guidance refers to external control arms being different in either time or setting. ACRO would welcome clarification on the use of external control arms which are different in both time and setting. ACRO would also welcome clarification on any other characteristics that differentiate external control arms from internal control arms.

Line 55

ACRO notes with interest the statement that *“for decades FDA has recognized the potential value of other types of controls”*. It would be helpful for the FDA to expand this statement to include examples of the potential value of other types of controls, beyond the statement on historical controls provided in CFR 314.126 2(v). In particular, guidance on any particular ethical considerations and operational consideration of when external controls could be appropriate would be welcome.

CRF314.126 2(v) states *“historical control designs are usually reserved for special circumstances. Examples include studies of diseases with high and predictable mortality (for example, certain malignancies) and studies in which the effect of the drug is self-evident (general anesthetics, drug metabolism).”* Further examples of clinical situations in which historical controls could be acceptable would be welcome.

Lines 103-148

ACRO would welcome further detail of situations where the use of the external control may be warranted as part of the design consideration. For example:

1. The use of an external control (created from patient level data with statistical techniques to balance baseline composition) in indications that traditionally have been studied with single arm trials and study level benchmarking

2. The use of an external control or hybrid design in indications where randomization may preclude enrolling or completing an interpretable randomized trial. For example, in extreme clinical situations where patients have no further active treatment options, patients are often reluctant to enroll in a randomized trial owing to the possibility of being assigned to the standard of care. In these situations, patients may discontinue early from a randomized trial after learning they have been assigned to the control therapy making the randomized trial very difficult to interpret.

Line 108

The current text reads:

“Specific design elements to prespecify in the protocol (i.e., before conducting an externally controlled trial) include suitable study data sources, baseline eligibility (inclusion and exclusion) criteria, appropriate exposure definitions and windows, well-defined and clinically meaningful endpoints, cogent analytic plans, and approaches to minimize missing data and sources of bias.”

The ICH E6(R2) guidance on Good Clinical Practice defines the protocol as *“A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents.”* Accordingly, ACRO recommends addition of the text highlighted in bold to make clear that the required information can be described in a separate document referenced in the study protocol:

*“Specific design elements to prespecify in the protocol, **or a separate document referenced in the protocol** (i.e., before conducting an externally controlled trial) include suitable study data sources, baseline eligibility (inclusion and exclusion) criteria, appropriate exposure definitions and windows, well-defined and clinically meaningful endpoints, cogent analytic plans, and approaches to minimize missing data and sources of bias.”*

Lines 340-343

ACRO would welcome clarification on how to evaluate whether results of an external control arm are *“inconsistent with prior experience”* and guidance on what documentation should be considered.

Lines 374 – 375

ACRO proposes adding a further *“Specific population – Pediatric Population”* as an additional Focus of Comparison with Considerations for Data Comparability to include *“It is important to ensure appropriate age group comparisons.”*

Lines 460-470

ACRO would suggest providing further emphasis on the potential importance of differential misclassification errors (when the probability of misclassification differs across study arms). ACRO suggest including the information currently in footnote 32 within the main text of lines 460-481.

Lines 506-513

ACRO notes that the present draft guidance states *“Sponsors must include in their marketing applications relevant patient-level data (i.e., data on each participant and patient in the externally controlled trial), as required under FDA regulations, for both the treatment and external control arms.”* The present draft guidance also requires *“ensur[ing] that FDA has access”* to the source data and documents, and recognizes that sponsors may not have such access to provide to FDA (*“If sponsors do not own the data used for the external control arm, they should structure their agreements with the data owners to [so] ensure”*).

The present draft guidance appears to present an expanded requirement for access to "source" documents and data as compared with NDA submissions, given that, compliance with 21 CFR 314.50(f), requires case report tabulations, and only certain, limited case report forms for NDA submissions (314.50(f)(2) and (f)(3)). In both cases (314.50(f)(2) and (f)(3)) only those case report forms "necessary" "for a proper review of the study" are required.

ACRO notes that regulation 21 CFR 601.2 concerns the "safety, purity, and potency" of the manufactured product itself, and is not apposite to the "proper review" of an external control arm. In addition, 21 CFR 601.2 is further directed to ensuring the protection of human subjects. The data of patients or participants comprising an external control arm may or may not be subject to IRB approval or waiver in the first instance; this part of the draft guidance does not appear to be apposite to the "proper review" of the external control arm.

ACRO notes there are different reasons that external control arm sponsors may not have access to source data and documents to provide to FDA. For example, under privacy laws in various countries, the sponsor may simply not be able to secure such access. As noted above, for conditions which are extremely rare in the USA and too rare for a viable US-only study, the only route to establish whether a new drug or vaccine works may be a study across different jurisdictions; however, the FDA may be legally unable to access the source data.

ACRO also notes that, where external control arm sponsors lack access to source data and documents to provide to FDA, a rigid requirement to provide source data and documents may obviate many or most current sources of patient and participant data for purposes of external control arms. The go-forward solution as proposed by FDA ("[sponsors] should structure their agreements with the data owners to [so] ensure"), even where possible, presents as unnecessarily resource-consuming, and critically, as likely to fail, e.g., where the external control arm sponsor is unable to re-contract with all data owners of the external control arm's source data.

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.

ACRO believes that, where external control arm sponsors may not have access to source data and documents to provide to FDA, the corresponding NDA submissions regulations' requirement that the applicant facilitate "proper review of the study" may still be satisfied. For example, for external control arms derived from historical clinical trial data, the sponsor may provide FDA with information and evidence supporting the integrity and validity of the external control arm data, as permitted by the data owners, and in compliance with both the letter of regulations covering NDA submissions (requiring only that data necessary "for a proper review of the study") and the policy goals of those regulations.

Such means are appropriate, inter alia, where the external control arm is comprised of synthetic data, e.g., as may be generated by approaches reflected in the NCAT'S Synthetic Data Workstream (see https://covid.cd2h.org/N3C_synthetic_data). This is because the generated synthetic data cannot, by



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definition, be traced back to source data. Instead, sponsors should be able to, and should be required to, demonstrate the validity and integrity of the generated synthetic data for a proper review of their submitted external control arm. ACRO would therefore welcome guidance on other means of compliance with the regulations.

Thank you for this opportunity to provide feedback. Please do not hesitate to contact ACRO (knoonan@acrohealth.org) if we can provide additional details or answer any questions.

Respectfully submitted,

Karen Noonan
Senior Vice President, Global Regulatory Policy