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FDA Issues Draft Guidance on "External Controls" in Clinical Trials to Support Safety and Efficacy of a Drug

The Food and Drug Administration (FDA) has issued new draft guidance, Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products (the "External Controls Draft Guidance"), that provides its current considerations regarding the use of external patient level data as the control arm in a clinical trial to demonstrate the effectiveness and safety of a drug. This complements FDA's prior guidance regarding the use of real-world data ("RWD") to develop real-world evidence ("RWE") in response to the mandate of the 21st Century Cures Act ("The Cures Act")[1]. The Cures Act addresses the use of RWE for two regulatory purposes: (1) to help support FDA approval of new indications for approved drugs; and (2) to satisfy certain postapproval study requirements for approved drugs. The 2018 "Framework for FDA's Real-World Evidence Program"[2], issued by CDER and CBER, briefly cites potential use of an "external RWD control" where RWD from patients outside of the trial would provide evidence as an external control in a single-arm prospective interventional drug study. However, in that document, FDA did not clarify whether an external control could potentially suffice to meet the legal requirement for "substantial evidence" of effectiveness to support new drug approval.[3,4]

The External Controls Draft Guidance provides FDA's thinking specifically with regard to a trial that has a single treatment arm and single control arm. The draft guidance proposes that in addition to a prospective randomized controlled trial ("RCT"), a trial using an external concurrent or historic control group can, when appropriate, serve toward "the adequate and well-controlled controlled clinical investigations generally required to provide substantial evidence of effectiveness" under section 505(d) of the FD&C Act. However, for the reasons discussed below, FDA cautions that in many instances such trials will not be appropriate. In particular, FDA explains, often "the likelihood of credibly demonstrating the effectiveness of a drug with an external control is low, and sponsors should choose a more suitable design."

KEY COMPONENTS OF FDA'S CONCERNS REGARDING USE OF AN EXTERNAL CONTROL

Consistent with FDA's prior guidance on the use of RWD to develop RWE for regulatory decision-making[5], the External Controls Draft Guidance clarifies that multiple sources of patient-level data could potentially serve as the control arm data in an externally controlled clinical trial, including but not limited to data from other clinical trials, registries, natural history studies, electronic health records ("EHR"), and medical claims data. The External Controls Draft Guidance emphasizes that summary-level data will not suffice for use in an externally controlled trial. FDA observes that it has previously relied on external controls on a case-by-case basis in clinical trials where there is a single prospective arm of patients assigned to the investigational drug. The draft guidance thus provides the example of use of historical control data in a disease where the natural history is well-defined and the disease is known not to improve with available therapies. This precedent has been well-established in clinical trials of rare inherited disorders in children. By way of further example, the draft guidance also cites single arm oncology trials where objective response rate is often used as an endpoint in trials for certain cancers for which shrinkage of the tumor rarely occurs without intervention. However, the External Controls Draft Guidance strongly emphasizes FDA's concern of threats to the validity of trial results from potential bias if an external control is used to demonstrate the effectiveness of a drug.

- **Determining if a difference in outcomes between groups can be attributed to investigational treatment** – The External Controls Draft Guidance emphasizes that a properly conducted RCT ensures the similarity of the treatment group and the control group regarding known variables and unknown factors that could potentially affect the efficacy outcomes that are being measured. This similarity of treatment and control groups, as well as the management of subjects and data collected during a RCT, is enhanced by: blinding of subjects (as well as investigators and sponsors) to the treatment assignment; application of identical inclusion and exclusion criteria to both groups; protocol-specified data to be collected and the timing for data collection; definitions of outcome events of interest; and methodology to minimize missing data. The drum beat of the draft guidance is FDA's skepticism that there will be sufficient similarity in patient populations and their management in an external control group and prospective treatment group and, as a result, efficacy outcomes may be uninterpretable. In addition to the lack of blinding, FDA identifies and defines three distinct issues that must be prospectively addressed by sponsors considering use of an externally controlled trial to demonstrate effectiveness of a drug.
  - **Unmeasured confounding**. Distortion of the measure of the effect of a drug treatment on an outcome due to another factor that results in an erroneous estimate of the treatment's effect on the outcome of interest (as examples, failure to consider potential prognostic attributes that could influence study outcome, such as performance status or comorbidities, or inability to account for such attributes in a comparable manner in the treatment and external control groups).
  - **Bias.** Any systematic error in the design, conduct, analysis, or interpretation of a study that results in an erroneous estimate of a treatment's effect on the outcome of interest (as examples, inadvertent or purposeful selection of an external control group or the final analytic dataset that favors a particular study result).
  - **Intercurrent events.** An event occurring after treatment initiation that affects either the interpretation or the existence of measurements associated with the clinical outcome of interest (as examples, switching or discontinuing treatment, use of rescue medications, or experiencing terminal events such as death).
- **Developing a prospective analysis plan for an externally controlled trial** – the External Controls Draft Guidance makes it clear that the analysis plan should be based on the demonstration of superiority and that a non-inferiority approach is not recommended. In selecting an external control group for comparison to patients in a prospective treatment arm, FDA provides a table of specific factors to consider regarding potential comparability of data.

To reduce the potential for bias in externally controlled trials, FDA's draft guidance recommends that sponsors should prospectively finalize both the proposed study protocol and the analytic approach prior to initiation of an externally controlled trial. Sponsors should prespecify specific design elements for both the treatment and external control groups including, but not limited to, identification of data sources; inclusion and exclusion criteria; definitions of specific time windows for start and stop of data collection (i.e., time zero for the start of observation period for assessment of endpoints); well-defined and clinically meaningful endpoints; explicit analytic plans; methods to minimize missing data; and methods to address sources of bias. FDA emphasizes the following recommendations for sponsors developing an analytical plan using an external control:

- **Provision of a justification for selecting or excluding data sources**. As a component of the analytic plan, FDA advises that sponsors should demonstrate that the specification of the final analytic dataset for the control arm was not chosen to favor specific study results. The draft guidance advises sponsors to prospectively generate audit trails to track access to and analyses done on data sources.
- **Confounding elements and sources of bias**. The draft guidance advises the prespecification of plans to measure and analyze data regarding important confounding factors and sources of bias.
- **Addressing the lack of blinding**. FDA recommends re-adjudication of externally controlled data by a blinded independent central review, noting that lack of blinding to treatments in an externally controlled trial can lead to biased estimate of the treatment effect. The Agency explicitly raises the concern that data and events in EHRs, such as worsening heart failure, may not be consistently captured in routine clinical care and may be misclassified or inaccurate.
- **Missing data.** FDA acknowledges that sound proposed analytical methods include an approach for missing data, which is particularly likely to affect the external control group. However, the draft guidance warns "Assumptions about missing data can be unverifiable and may be difficult to justify, in addition to other assumptions required for estimation of treatment effect in a non-randomized setting."
- **Statistical analysis**. Notably, the draft guidance does not affirmatively recommend a favored statistical analytic approach, nor does it provide any assurance that current statistical techniques for propensity matching are likely to resolve potential deficits in comparability of the prospective treatment group and external control group.

- **Actions to support FDA regulatory review** – The draft guidance emphasizes that sponsors should consult with the relevant review division early in a drug development program if the sponsor is considering an externally controlled trial rather than a RCT. We infer from FDA's reference to the period of early drug development that FDA is particularly concerned about use of an externally controlled trial to support approvals of new drugs.
  - **IND pre-submission discussion**. Sponsors should be prepared to present detailed information regarding why the proposed externally controlled study design is appropriate, a description of the proposed external control data sources and why they are "fit for use," the proposed statistical analysis, and plans to address FDA's expectations for data submission.
  - **Contractual agreements with patient-level data owners to ensure FDA access**. The draft guidance also recommends that if a sponsor does not own the patient-level data for the proposed external control group, the sponsor should ensure that a contractual agreement is in place with the data owner so that (i) patient-level (anonymized) data can be submitted to FDA in the marketing application; and (ii) source documents and source data for the external control are available for inspection by FDA.

SUMMARY

The External Controls Draft Guidance opens the door a crack regarding the potential for the use of an external control group for comparison with a prospective treatment group, rather than a prospective RCT, as evidence of safety, as well as "substantial evidence" of effectiveness for a new drug. Based on historic precedent at FDA, the Agency may consider this clinical trial strategy to be acceptable particularly for drugs intended to treat rare diseases with very well-defined patients and natural history, such as certain childhood inherited disorders, and also potentially for advanced cancers in which disease progression is rapid and tumor shrinkage is not expected. However, the draft guidance also exposes FDA's concerns regarding ensuring similarity of the treatment and external control groups as well as the potential impact of bias, unmeasured confounding, and lack of blinding on estimation of the treatment effect. Therefore, the External Controls Draft Guidance does not indicate a robust willingness by FDA to accept use of externally controlled trials as sufficient to support findings of safety and "substantial evidence" of efficacy for new drugs.

FDA requests submission of comments by May 2, 2023 that should be identified with the document's docket number: FDA-0022-D-2983.

If you have questions regarding the draft guidance or would like assistance in preparing comments, please contact Beverly Lorell, Chris Markus, or Eva Temkin for more information.

[1] Public Law 114-155 (enacted December 13, 2016). The Cures Act added section 505F to the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. § 355g).
[2] "U.S. Food and Drug Administration. Framework for FDA's Real-World Evidence Program." December 2018. *See* page 20. Accessed at https://www.fda.gov/media/120060/download.
[3] *See* section 505(d) of the FD&C Act (21 U.S.C. § 355(d)): "…[T]he term 'substantial evidence' means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence for purposes of the preceding sentence."
[4] *See* 21 C.F.R. § 314.126 (elucidation of "adequate and well-controlled studies").
[5] Accessed at https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence.