Two Recent FDA Guidances Impact Use of Registries for Research

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This summer, FDA released two guidances that sponsors should be aware of when using registry data to support clinical research or when contributing study results to prospective registries. The FDA guidance on Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices (August of 2017) (RWE Guidance) contains many examples of how registries can be used to support FDA submissions.

This guidance dovetails with the FDA guidance on IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More Than Minimal Risk to Human Subjects (July 2017) (IRB ICF Guidance). These FDA guidances may impact manufacturers from both business and clinical perspectives on whether and how to create, contribute data to and use registries.

Creating a well-designed registry takes significant forethought and planning. A number of factors combine to create a well-balanced registry design, such as having appropriate data governance (e.g. data ownership, access and sharing), objectives, evidence assessment, data minimization, regulatory compliance, funding and more. For more information, see the Clinical Trials Transformation Initiative (CTTI) document entitled, CTTI RECOMMENDATIONS: REGISTRY TRIALS, and the AdvaMed Registry Principles. CTTI is a public-private consortium co-founded by FDA and Duke University.

Leveraged properly, registry data can create efficiencies in the product development and approval processes, as well as postmarket compliance.

RWE Guidance

Section VI of the Real-Word Evidence (RWE) guidance gives generalized illustrations of how real-world evidence, which is derived from real-world data (RWD), has actually been used to support regulatory decision making. FDA provides examples of how registries are used in each of the following:

A. Expanded indications for use

B. Postmarket surveillance studies (Section 522)

C. Post-Approval device surveillance as a condition of approval

D. Control group

E. Supplementary data

F. Objective performance criteria and performance goals (no specific registry examples here).

Manufacturers that start planning early enough can create registries that will not only help speed regulatory decisions but could save the manufacturer time and money in gathering data needed for FDA requirements. See this example from Section VI.C:

> For example, a new breakthrough Class III medical device was approved based on prospective, randomized, and controlled clinical trial data. Early in the PMA review process, the manufacturer began to consider postmarket commitments, and began discussions with FDA and other stakeholders. A registry was launched that generated RWD that could meet FDA's data requirements, as well as others. Because the new registry was constructed early enough to collect information about all patients receiving this device upon approval, FDA could provide an earlier device approval conditioned on further robust RWD collection and reporting in the postmarket setting. This registry has since been used to a) collect surveillance data on subsequent devices with similar designs and indications, b) collect and retrospectively analyze RWD on all uses of the devices to support new expanded indications for use, and c) support embedded prospective clinical investigations under IDE for new devices and new generations of approved devices. No IDE is necessary for the general data collection activities of the registry, as it collects RWD on all uses of otherwise approved medical devices and it does not influence the treatment decisions and/or follow-up care that patients receive. The retrospective analysis of RWD for uses that are outside the approved indications for use did not require an IDE because treatment decisions were not influenced by the expectation of conducting the future analysis, but was still reviewed by an IRB for human subject protection issues.

Section V discusses data relevance and reliability, both of which are essential to using RWD as RWE. For example, Section VB(2) refers to a number of published recommendations concerning quality control for registries.

The RWE Guidance also discusses when an IDE may be necessary with regard to the creation or use of the registry. Regardless of whether an IDE is necessary, the RWE Guidance makes clear that IRB review, informed consent and financial disclosure, as well as other laws on human subject protection, may apply to RWE generation activities.

IRB ICF Guidance

In the IRB ICF Guidance, FDA announces its intention not to object to an IRB's waiver or alteration of informed consent requirements for FDA-regulated minimal risk studies that have adequate human subject protections. The IRB must find and document that:

1. **The clinical investigation involves no more than minimal risk (as defined in 21 CFR 50.3(k) or 56.102(i)) to the subjects;**
2. **The waiver or alteration will not adversely affect the rights and welfare of the subjects;**
3. **The clinical investigation could not practicably be carried out without the waiver or alteration; and**
4. **Whenever appropriate, the subjects will be provided with additional pertinent information after participation.**

The IRB ICF Guidance goes on to explain that FDA does not intend to object to a sponsor initiating, or an investigator

conducting, a minimal risk investigation under these circumstances.

The IRB ICF Guidance takes effect immediately (it will be withdrawn after FDA promulgates regulations on the topic) and aligns FDA's policy on waiving informed consent with the Common Rule, which has permitted waiver since 1991.

The IRB ICF Guidance is expected to facilitate drug, device and biologic manufacturers in collecting RWD and RWE from low-risk research activities, such as observational studies or registries, and using those results to support FDA submissions.

If you have any questions or would like more information about these developing issues, please contact the following:

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