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Clinical Trial Regulation Requirements: Navigating the Landscape

The landscape of clinical trial registration requirements has changed significantly in recent years, and the various policies and requirements for registering clinical trials raise several practical issues for research sponsors, institutions and investigators.

In 1997, the Food and Drug Administration Modernization Act (FDAMA) established the online registry ClinicalTrials.gov, but required registration only of certain drug trials for serious or life threatening diseases. A subsequent major catalyst for development in this area was the policy of the International Committee of Medical Journal Editors (ICMJE), initially adopted in 2004, which requires public registration of clinical trials as a condition of publication in any ICMJE-participating journal.[1]

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Since the establishment of the registration requirements under the FDAMA in 1997 and promulgation of the ICJME registration policy in 2004, the demand for public registration of clinical trials has grown both within and outside of the U.S. The U.S. Congress under the Food and Drug Administration Amendments Act of 2007 (FDAAA) significantly expanded the U.S. legal requirements for registering clinical trials by requiring registration of most Phase II, Phase III and Phase IV drug and device trials on ClinicalTrials.gov. In addition, through recent legislation and guidance, the European Medicines Agency (EMA) now makes certain information from its EudraCT clinical trials database publicly available on a separate database called EudraPharm. Historically, information in the EudraCT database was available only to government authorities and certain funding agencies. Other stakeholders in both the U.S. and abroad have also established clinical trial registration requirements and policy statements. Understanding these various policies and requirements and how, or whether, they apply to a given study can be challenging. We address below some of the issues concerning clinical trial registration that affect research sponsors, institutions and investigators.

- **Is the ICMJE clinical trial registration policy mandatory?**

  The ICMJE clinical trial registration policy is, from a strictly legal perspective, voluntary. It does not carry the force of law or regulation and sponsors, institutions and investigators may elect not to comply with the policy without the risk of legal sanctions or penalties. However, the implications of not registering a clinical trial in accordance with the ICMJE policy makes compliance with the policy mandatory as a practical matter for many sponsors, institutions and investigators.

  The consequence of not registering a clinical trial in accordance with the ICMJE policy is ineligibility for publication in all ICMJE-participating journals. Several other journals now have policies similar to the ICMJE's, so publication in other journals may also be precluded. Given the importance of publication in the academic, medical and research communities, most institutions and investigators are unwilling to conduct a clinical trial which they know from the outset is not eligible for publication. Accordingly, sponsors of clinical trials may be asked to agree in the clinical trial agreement to register the trial in accordance with the ICMJE policy. A sponsor who is unwilling to do so may find it difficult to engage a sufficient number of qualified investigators to conduct a clinical trial. Consequently, compliance with the ICMJE policy is of significant importance to institutions and investigators that want to publish and for the sponsors who rely on them to conduct clinical trials.

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- **Are the federal registration requirements under the FDAAA the same as the requirements under the ICMJE policy?**

  Though similar, the FDAAA and ICMJE requirements differ in some respects. Some of the key differences between these two sets of registration requirements are as follows:

  - **Phase I trials.** The FDAAA requires registration of most Phase II through Phase IV drug and device trials (referred to in the FDAAA and subsequent FDA and NIH guidance as "applicable clinical trials"). The ICMJE goes beyond the requirements of the FDAAA by requiring registration of "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes," which may include Phase I clinical trials.

  - **Designated registry.** Applicable clinical trials under the FDAAA must be registered on ClinicalTrials.gov. The ICMJE, however, permits registration on ClinicalTrials.gov or one of several other public registries, including any of the primary registries that participate in the World Health Organization's International Clinical Trial Registry Platform.

  - **Timing.** The ICMJE policy is more stringent than the FDAAA regarding timing of registration. While the FDAAA permits registration up to 21 days after the first study subject is enrolled, the ICMJE requires registration before the first subject is enrolled. As a result, registration in the U.S. of a clinical trial, if not carefully timed, may not satisfy the ICMJE requirements, notwithstanding that the trial is registered in accordance with U.S. law. Deadlines for updating information also differ. With some exceptions, the FDAAA generally requires the information on ClinicalTrials.gov to be updated at least every 12 months. The ICMJE, on the other hand, requires updates at least every six months.

  - **Consequences of non-compliance.** As noted above, failing to register a clinical trial in accordance with the ICMJE requirements means that the trial is ineligible for publication in ICMJE-participating journals. The consequences of noncompliance with the FDAAA registration requirements are more severe and include civil monetary penalties of up to $10,000 and, for federally-funded trials, withholding of or recovery of federal funds.

- **Does the FDAAA require registration of clinical trials conducted exclusively outside of the United States?**

  Clinical trials frequently are conducted on an international scale. This raises interesting questions about the applicability of the FDAAA registration requirements to trials conducted exclusively outside of the United States. The FDA's current thinking is this: If a clinical trial (1) has one or more sites in the U.S., or (2) involves a drug, biologic or device that is manufactured in the U.S. (or its territories), or (3) is conducted under an investigational new drug application (IND) or investigational device exemption (IDE), the FDAAA applies and the trial must be registered accordingly. By reverse inference, this means that if the drug or device is manufactured outside of the U.S. and its territories and the trial is conducted *exclusively* outside of the U.S. and its territories and does not require an IND or IDE, the clinical trial is not subject to the FDAAA registration requirements.

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Nevertheless, the sponsor of a clinical trial that is not subject to the FDAAA registration requirements may want to consider registering the trial in accordance with the FDAAA. It has been suggested that the results of a foreign study that was not registered pursuant to the FDAAA may not be eligible for consideration by the FDA in certain future submissions such as INDs, new drug applications, and premarketing approval applications. Therefore, if there is any possibility of future submission to the FDA of results of a foreign study that is otherwise not subject to the FDAAA, the sponsor may wish to register as a matter of prudence.

Aside from the FDAAA, sponsors, investigators and institutions must be cognizant of and comply with any local and/or regional registration requirements that may apply.

- **Are there particular challenges or issues that arise in the context of registration of multi-center clinical trials?**

For registration of multi-center clinical trials, coordination is key. Because there are multiple investigators and institutions in a multi-center clinical trial, there is an increased risk of duplicate registration, which may lead to incorrect or inconsistent information being posted. The FDA recommends that registration of a multi-center trial be coordinated by the sponsor of the trial (or lead sponsor, if there is more than one) to avoid duplication of efforts and to ensure that data are registered accurately.

In addition, studies that are conducted in a variety of geographic regions may be subject to multiple registration requirements. If any sites in a multi-center clinical trial are located in a state or region with separate registration requirements, the sponsor of the trial (and perhaps others) must be cognizant of, and ensure compliance with, any such requirements. This may require extra vigilance and coordination to address, for example, differences in the information that is required to be registered and the deadlines for updating information in the various registries.

Evolving clinical trial registration laws and policies will present new issues and questions for organizations and investigators that sponsor and conduct clinical research.

[1] The ICMJE participating journals include: *Annals of Internal Medicine*, *British Medical Journal*, *Canadian Medical Association Journal*, *Croatian Medical Journal*, *Journal of the American Medical Association*, *Nederlands Tijdschrift voor Geneeskunde (The Dutch Medical Journal)*, *New England Journal of Medicine*, *New Zealand Medical Journal*, *The Lancet*, *The Medical Journal of Australia*, *Tidsskrift for Den Norske Lægeforening (The Journal of the Norwegian Medical Association)*, *Ugeskrift for Laeger (Journal of the Danish Medical Association)*, the U.S. NLM, and the World Association of Medical Editors.