New HHS clinical trials registry regulations set to go into effect in January 2017: top points in one chart

FDA Alert
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Nearly a decade after Congress directed significant expansion of the national clinical trials database, www.ClinicalTrials.gov, the US Department of Health and Human Services (HHS) has issued final implementing regulations (the Final Rule).

Weighing in at 177 pages, and informed by nearly 900 comments, the Final Rule, issued in late September, aims to improve public access to information about specified clinical trials involving FDA-regulated products.

The Final Rule both implements and elaborates on the requirements of the 2007 Food and Drug Administration Amendments Act (FDAAA) and provides a specific deadline by which "responsible parties" (*i.e.,* sponsors and investigators of clinical trials) must come into compliance. Under the Final Rule, responsible parties will be required to submit additional information when registering, update registration within specified timelines in response to new information, and report on a wider range of adverse events. The Final Rule also expands the categories of clinical trials for which results must be submitted, and specifies penalties for non-compliance, including civil and criminal enforcement action by FDA.

Concurrent with the Final Rule, the National Institutes of Health issued a final policy that extends registration and reporting requirements to all NIH-funded clinical trials , including Phase 1 drug trials and small feasibility trials for medical devices.

History

ClinicalTrials.gov is a publicly accessible clinical trial registry operated by the National Library of Medicine, within the NIH. The registry contains information submitted by "responsible parties" (*i.e.*, sponsors or principal investigators) about "applicable clinical trials," being conducted with certain drugs, biologics, and medical device products. First established nearly two decades ago, pursuant to the Food and Drug Administration Modernization Act of 1997 (FDAMA), the success of ClinicalTrials.gov has been hampered by the limited amount of information submitted, lack of clarity regarding registration requirements, and lack of enforcement.

Congress sought to address these concerns in the FDAAA which, among other changes, broadened the scope of reportable trials to include medical device clinical trials, specified additional information that must be submitted at the time of registration, and required the submission of data concerning clinical trial results and adverse events. FDAAA also authorized the imposition of penalties for non-compliance including withdrawal of NIH grant funding and assessment of civil monetary penalties.

FDAAA directed the implementation of these new requirements within three years of enactment. Although NIH held a public meeting to gather input on implementation in 2009, a proposed rule was not issued until 2014. In the absence of implementation, compliance, in particular with respect to disclosing clinical trial results, remained low. Furthermore, notwithstanding the penalty provisions contained in FDAAA, there were few practical consequences to non-compliance.

Final Rule's top points

The Final Rule codifies and expands on the requirements specified in FDAAA. The table below highlights key clarifications and changes. In particular, the Final Rule:

- Clarifies that there is only one responsible party for each clinical trial, on whom the compliance obligations ultimately rest
- States that the sponsor will be designated the responsible party in ClincalTrials.gov unless the sponsor affirmatively designates the principal investigator as the responsible party at the time of registration
- Clarifies that if the principal investigator is no longer able to meet the requirements of responsible party, the sponsor will automatically become the responsible party unless and until s/he designates another principal investigator
- Expands the definition of "applicable clinical drug trial" to include trials of combination (e.g., drug/device) products
- Specifies additional descriptive information to be included at the time of registration, including whether the investigational product is currently subject to regulation by FDA, and the study's expected completion date
- Requires reporting of all deaths of study subjects, regardless of cause
- Expands the scope of clinical trials for which results must be submitted to include drugs or devices that are not approved, licensed, or cleared by the FDA, regardless of whether approval was sought
- Codifies the statutory penalties specified in FDAAA, which have largely been unenforced, into new Section 11.66

Requirement	Section 801 of FDAAA (2007)	Final Rule (Effective January 17, 2017)
Registration by "responsible party"	Responsible party can be either the sponsor or the principal investigator of the clinical trial.	Clarifies that although the sponsor may designate the PI as the responsible party, the sponsor is obligated to ensure the PI's qualifications, and, if PI can no longer meet requirements, the sponsor will automatically be designated the responsible party unless and until the sponsor designates another PI as the responsible party. Also clarifies that there is only one responsible party for each clinical trial.
Scope of "applicable drug clinical trial"	Defined as "a controlled clinical investigation, other than a phase 1 clinical investigation, of a drug product or a biological product."	Broadens scope to include clinical trial of a combination product where the drug is the primary mode of action.
Scope of "applicable device clinical trial"	Defined as (1) a prospective clinical study of health outcomes comparing an intervention with a device	Broadens scope to include clinical trial of a combination product where the device is the primary mode of action.

	subject to section 360(k), 360e, or 360j(m) of Title 21 against a control in human subjects; (2) a pediatric postmarket surveillance study.	
Information that must be submitted upon registration	Descriptive Information • Brief title • Brief summary • Primary purpose • Study design • For an applicable drug clinical trial, the study phase • Study type • Primary disease or condition being studied, or the focus of the study • Intervention name and intervention type • Study start date • Expected completion date • Target number of subjects • Outcomes, including primary and secondary outcome measures	Additional Descriptive Information • Official title • Pediatric postmarket surveillance of a device product, for an applicable device clinical trial that is a Pediatric Postmarket Surveillance of a Device Product • Other Intervention name • Intervention Description, for each intervention studied • Studies a US FDA-regulated Device Product • Studies a US FDA-regulated Drug Product • Device Product not approved or cleared by US FDA, if any studied intervention is a device product • Post prior to US FDA approval or clearance, for an applicable device clinical trial that studies at least one device product not previously approved or cleared by the US FDA • Product manufactured in and exported from the US • Expected completion date is now branched into Primary Completion Date and Study Completion Date • Enrollment
	Recruitment information • Eligibility • Gender • Age limits • Whether trial accepts healthy volunteers • Overall recruitment status • Individual site status • In the case of applicable drug clinical trial, if the drug is not approved	Additional Recruitment Information • Why study stopped • Availability of expanded access
	Location and contact information • Name of sponsor • Responsible party • Facility name and facility contact information	No additional information required
	Administrative data • Unique protocol identification number	No additional information required

	• Other protocol identification numbers • FDA IND/IDE protocol number and the record verification date	
Submission of summary clinical trial results	Results must be submitted for applicable drug clinical trials of FDA-approved products	Results must also be submitted for clinical trials of drugs or devices that are not approved, licensed, or cleared by the FDA, regardless of whether approval was sought.
Submission and timing of updates	Changes to the clinical trial information	For applicable device clinical trials of unapproved or uncleared device products, the responsible party must update the following data elements within the specified time frame. • Intervention name must be updated not later than 30 days after a non-proprietary name is established. • Primary completion date must be updated not later than 30 days after clinical trial reaches actual primary completion date. • Study completion date must be updated not later than 30 days after it reaches its actual study completion date. • Overall recruitment status must be updated not later than 30 days after any change in overall recruitment status (suspended, terminated, or withdrawn). • Record verification date must be updated any time the responsible party reviews the complete set of submitted clinical trial information for accuracy
Quality control mechanisms to verify submitted information	No formal mechanism specified. The law provided that a pilot quality control project would be conducted to determine optimal method.	• The NIH may send an electronic notification to the responsible party if there are any apparent errors, deficiencies, and/or inconsistencies in the submitted information identified during procedures for quality control review. • A responsible party who becomes aware of errors must submit a correction.
Submission of adverse event information	• Anticipated and unanticipated serious adverse events grouped by organ system • Anticipated and unanticipated adverse events that exceed a frequency of 5% within any arm of the clinical trial, group by organ	In addition to the serious and frequent adverse events, all deaths, regardless of cause, must be reported.

	system	
Consequences of noncompliance	• Enacted new section 21 U.S.C. § 331(jj), which makes it a "prohibited act" subject to the penalties of 21 U.S.C. § 333 to: • fail to submit required certification of compliance or knowingly submit a false certification • fail to submit clinical trial information or submit false or misleading information to registry • Authorized NIH director to publish notices of violations in the registry • Authorized heads of HHS agencies authority to withhold grant funding for noncompliance • Codifies statutory penalty provisions in new Section 11.66, thereby giving added prominence to FDA's enforcement authority for noncompliance with clinicaltrials.gov	

While issuance of the Final Rule presents the end of a long road since the passage of FDAAA, stakeholders now must − in short order − review their current compliance programs to ensure they reflect the requirements of the Final Rule. DLA Piper will continue to monitor and inform our clients of new developments as FDA and NIH issues guidance documents and other materials to facilitate implementation.

The HHS Final Rule will be codified at 42 C.F.R. Part 11. Together with the NIH Policy, it will become effective on January 18, 2017, and responsible parties must come into compliance by April 18, 2017, or 90 days after the effective date.

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