

Clinical Trials Reporting

FDAAA Final Rule & NIH Policy Update



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NEWS RELEASES

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HHS takes steps to provide more information about clinical trials to the public



In an effort to make information about clinical trials widely available to the public, the U.S. Department of Health and Human Services today issued a [final rule](#) **pdf** that specifies requirements for registering certain clinical trials and submitting summary results information to ClinicalTrials.gov. The new rule expands the legal requirements for submitting registration and results information for clinical trials involving U.S. Food and Drug



Institute/Center

[NIH Office of the Director \(OD\)](#)

Contact

[NIH News Media Branch](#)
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Additional Information

- [Federal Register Notice: HHS Final Rule](#) **pdf**
- [Federal Register Notice: NIH Policy](#) **pdf**
- [Summary of Changes: HHS Final Rule and NIH Policy](#)
- [Summary Table: HHS Final Rule and NIH Policy](#)
- [JAMA: Toward a New Era of Trust and Transparency in Clinical Trials](#)
- [NEJM: The Final Rule for US](#)

Recent Federal Clinical Trials Policies (September 2016)

- **FDA Amendments Act of 2007 - Final Rule** (Federal Register 9-21-16)

Clarifies the statutory language and expands transparency beyond the basic requirements.

- **NIH Policies**

- **NIH Policy on Dissemination of NIH-Funded Clinical Trial Information (NOT-OD-16-149)**

Extends the FDAAA ClinicalTrials.gov registration and reporting requirement to *all* NIH-funded clinical trials.

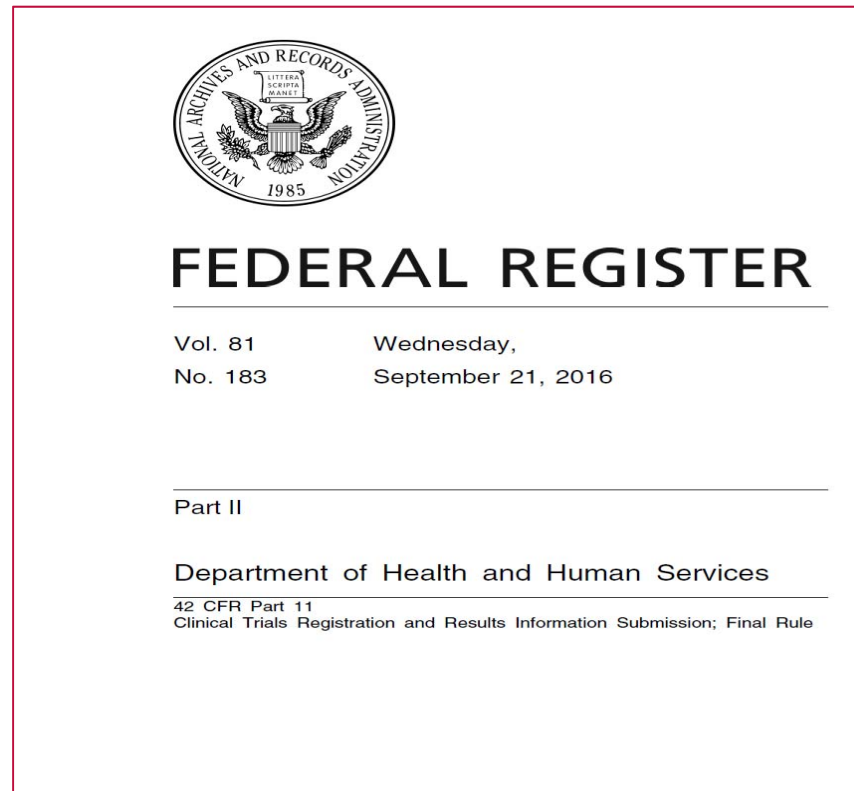
- **NIH Policy on Funding Opportunity Announcements for Clinical Trials (NOT-OD-16-147)**

NIH policy requires that all applications involving one or more clinical trials be submitted through a Funding Opportunity Announcement specifically designed for clinical trials.

- **NIH Policy on Good Clinical Practice Training (NOT-OD-16-148)**

All NIH-funded investigators and staff who are involved in the conduct, oversight, or management of clinical trials should be trained in good clinical practice.

Trial Reporting in ClinicalTrials.gov – The FDAAA Final Rule



FDA Amendments Act of 2007 (FDAAA)

- Title VIII of the **Food and Drug Administration (FDA) Amendments Act of 2007** (FDAAA) mandated the *registration and reporting of results* for applicable clinical trials.
 - **Applicable Clinical Trials (ACT)** generally include *interventional studies* (other than phase 1) of FDA-regulated drugs, biological products, or devices.
- **Sponsor:** primary organization overseeing implementation of study and responsible for data analysis.
- **Responsible Party:**
 - Sponsor, or a sponsor-designated PI responsible for conducting the study, has access to and control over the clinical data to analyze and publish the results.
- **Penalties established** for non-compliance, including civil monetary penalties and, for federally funded studies, the withholding of grant funds.

FDAAA Final Rule – Applicable Clinical Trials

- **Applicable clinical trials**

(1) clinical trials of drug and biological products that are controlled, clinical investigations, other than phase 1 investigations, of a product subject to FDA regulation; and

(2) prospective clinical studies of health outcomes comparing an intervention with a device product against a control in humans (other than small feasibility studies)

(3) any pediatric post-market surveillance studies required by FDA under the FD&C Act.

- Applies to studies with at least one U.S. location and/or using a product manufactured in and exported from the U.S.
- Does not apply to phase 1 trials or small feasibility device studies.

<https://www.nih.gov/news-events/summary-table-hhs-nih-initiatives-enhance-availability-clinical-trial-information>

FDAAA Final Rule 2016 – Select Key Points

- **Clarifies the statutory language**
 - Provides objective, structured criteria for evaluating whether a study is an ‘applicable clinical trial’ (ACT)
- **Expands transparency beyond the basic statutory requirements – requires submission of:**
 - results information for ACTs of *unapproved products*
 - baseline information on race or ethnic group, if collected during the clinical trial, and other characteristics associated with primary outcome
 - information about *adverse-event timeframe* and collection methods, as well as *all-cause mortality*
 - *full protocol* and statistical analysis plan at the time results submission
- **NIH will post all submitted information within 30 days of receipt regardless if a trial meets NIH quality-control review**

NEJM 2016; 376:1998-2004

NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information

Notice Number: NOT-OD-16-149

Key Dates

Release Date: September 16, 2016

Effective Date: January 18, 2017

Related Announcements

[NOT-OD-15-019](#)

Issued by

National Institutes of Health ([NIH](#))

Purpose

Summary

The National Institutes of Health (NIH) is issuing this policy to promote broad and responsible dissemination of information from NIH-funded clinical trials through ClinicalTrials.gov. The policy establishes the expectation that all investigators conducting clinical trials funded in whole or in part by the NIH will ensure that these trials are registered at ClinicalTrials.gov, and that results information of these trials is submitted to ClinicalTrials.gov. The policy is complementary to the statutory and regulatory reporting requirements. These are section 402(j) of the Public Health Service Act, as amended by Title VIII of the Food and Drug Administration (FDA) Amendments Act of 2007 (FDAAA), and the regulation Clinical Trial Registration and Results Information Submission, at 42 CFR Part 11. Hereafter, we refer to section 402(j) as the statute and 42 CFR Part 11 as the rule or regulation. This [policy](#) as well as the [rule](#) were posted in the Federal Register.

Supplemental Information

On November 19, 2014, and in tandem with the publication of the Notice of Proposed Rulemaking (NPRM) on Clinical Trial Registration and Results Submission, the NIH issued a complementary draft policy for public comment on the Dissemination of NIH-funded Clinical Trial Information^{1,2}. The draft policy proposed that all NIH-funded awardees and

NIH Policy NOT-OD-16-149

Dissemination of NIH-Funded Clinical Trial Information

- For NIH-funded clinical trials, extends ClinicalTrials.gov registration and reporting requirements to *all* clinical trials regardless of study phase or type of intervention.
 - *Includes behavioral and phase 1 trials*
- Applies to clinical trials funded in whole or in part through NIH extramural and intramural programs.
 - Does not apply to a clinical trial that uses NIH-supported infrastructure but does not receive NIH funds to support the conduct of the trial.
- Effective date – January 18, 2017 (study start date \geq 1/18/17 AND funding application first submitted \geq 1/18/17)

Effective Date – January 18, 2017

- **FDAAA Final Rule Requirements**

- Registration: Study Start Date \geq January 18, 2017
- Summary Results: Primary Completion Date \geq January 18, 2017

- **NIH Policy Requirements**

- Study Start Date \geq January 18, 2017

AND

- Funding application (e.g., grants, other transactions, contracts) first submitted \geq January 18, 2017

Key Clinical Trial Reporting Requirements

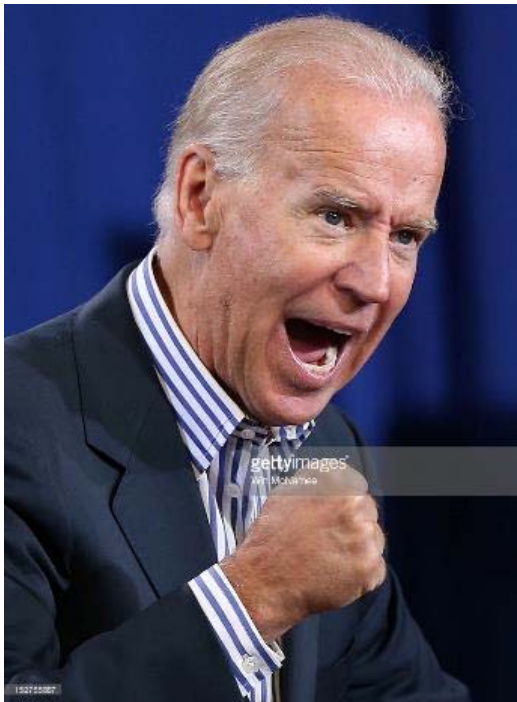
Reporting Requirement	ICMJE Policy (Effective in 2005)	FDAAA 2007 (Final Rule Issued in 2016)	Final NIH Policy (Issued in 2016)
Scope	Registration	Registration & Results Reporting	Registration & Results Reporting
Phase	All	≥ Phase 2	All
Intervention Type	All	Drugs, Biologics, & Devices regulated by the FDA	All (e.g., including behavioral interventions)
Funding Source	Any	Any	NIH
Enforcement	Refusal to publish	Criminal proceedings and civil penalties (up to \$10,000/day); Loss of HHS funding	Loss of NIH funding
Effective Date	2005	January 18, 2017	January 18, 2017

<https://www.nih.gov/news-events/summary-table-hhs-nih-initiatives-enhance-availability-clinical-trial-information>



Results Reporting Compliance

Enhancing Clinical Trial Transparency ClinicalTrials.gov

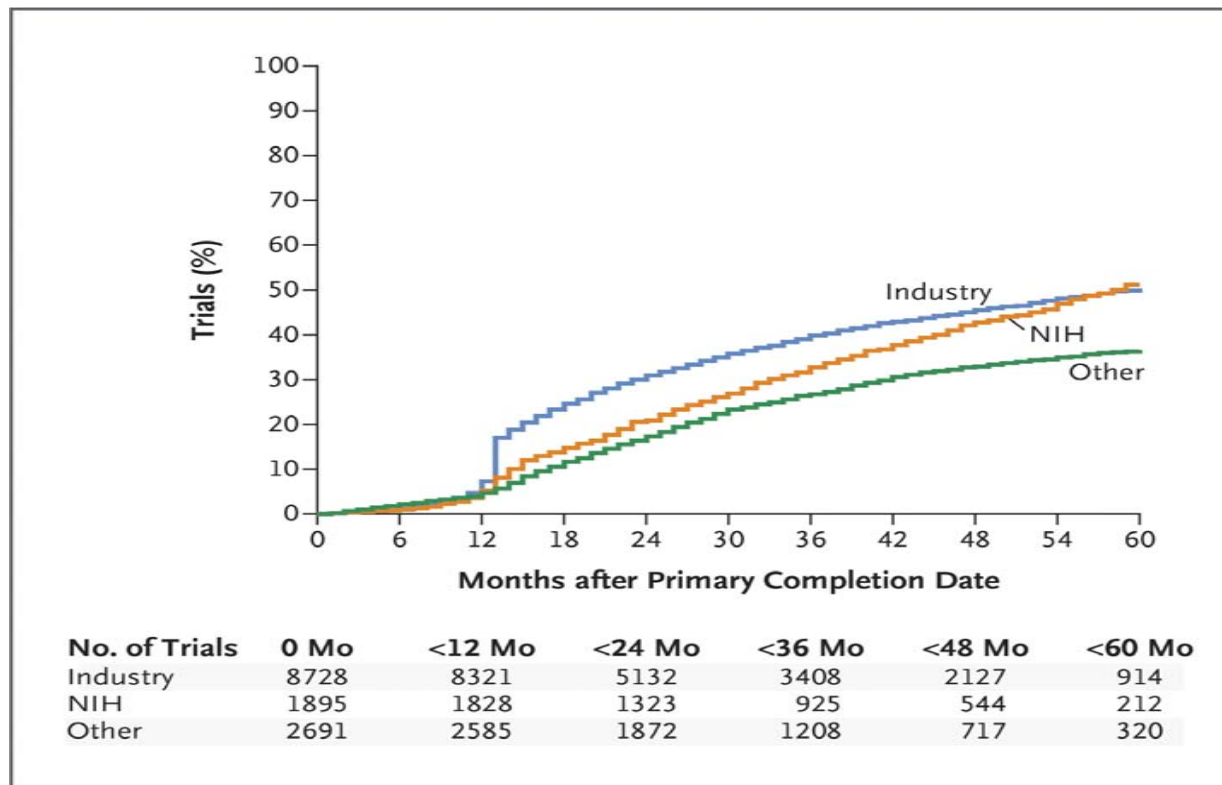


Under the law, it says you must report. If you don't report, the law says you shouldn't get funding. I'm going to find out if it's true [that the research centers aren't reporting the results] and if it's true, I'm going to cut funding. That's a promise.

Vice President Joe Biden

June 29, 2016

Cumulative Percentage of Clinical Trials That Reported Results to ClinicalTrials.gov According to the Time after the Primary Completion Date



[N Engl J Med.](#) 2015 Mar 12;372(11):1031-9

FDAAA “Basic” Results Reporting for NCI Sponsored and NCI Funded Trials as of 11/1/2016

	# of Registered (pACTs)***	# Registered Trials (“pACTs”) That May Need Results		% Reporting Results
		Total*	Reporting Results**	
NCI--sponsor	1,035	652	601	92%
Other NCI funded	2,690	1,609	711	44%

*Total = [Non-phase 0/1 interventional studies AND (IND or IDE OR a drug, biologic, or device AND at least one US site) AND completed after December 2007] AND [Primary Completion Date ≥ 1 Year]

**Reporting Results = Trials for which summary results are posted or submitted to ClinicalTrials.gov OR delayed submission of results are acceptable (i.e. submission of a certification or an extension request)

***pACT = probable applicable clinical trial

Data courtesy of Deborah Zarin, Director of ClinicalTrials.gov, NLM

FDAAA “Basic” Results Reporting by Top 10 NIH FY14 Grant Recipients

Sponsor Rank	# Registered Trials (“pACTs”) That May Need Results		% Reporting Results
	Total	Reporting Results	
1	106	24	23%
2	103	80	78%
3	136	20	15%
4	102	35	34%
5	102	90	88%
6	87	36	41%
7	43	28	65%
8	97	23	24%
9	59	12	20%
10	138	12	9%

Data courtesy of Deborah Zarin, Director of ClinicalTrials.gov, NLM ¹⁶

STAT News – December 13, 2015



- Assessed whether institutions reported results and whether they were reported “on time”
 - Analysis included trials of unapproved drugs or devices (if a certification was not on file)
- “The worst offenders included four of the top 10 recipients of federal medical research funding from the National Institutes of Health: Stanford, the University of Pennsylvania, the University of Pittsburgh, and the University of California, San Diego.”

High-level Implications of Recent Policies

- Transparency
 - Traditionally, investigators decided whether, when, and how to report results
 - Current policies promote systematic reporting of trial information
- Accountability
 - Organizations that sponsor studies will be held responsible for their conduct and reporting
 - Requires fundamental changes throughout the CRE: funders, sponsors, investigators
 - Key Message:
The time to decide if study is worth reporting is BEFORE the participants are put at risk, not AFTER
- Leadership is key!

Resources

- HHS takes steps to provide more information about clinical trials to the public
<https://www.nih.gov/news-events/news-releases/hhs-take-steps-provide-more-information-about-clinical-trials-public>
- Summary of HHS/NIH Initiatives to Enhance Availability of Clinical Trial Information
<https://www.nih.gov/news-events/summary-hhs-nih-initiatives-enhance-availability-clinical-trial-information>
- Hudson, KL et al. Toward a New Era of Trust and Transparency in Clinical Trials. JAMA. 2016;316(13):1353-1354
<http://jamanetwork.com/journals/jama/fullarticle/2553888?guestAccessKey=554e0981-9434-45f2-b122-d0e673cd1182>
- Zarin, DA et al. Trial Reporting in ClinicalTrials.gov – The Final Rule. NEJM 2016; 376:1998-2004.
<http://www.nejm.org/doi/full/10.1056/NEJMSr1611785>
- Final Rule webinar series
<http://clinicaltrials.gov/ct2/manage-recs/present>

SPECIAL REPORT

Trial Reporting in ClinicalTrials.gov — The Final Rule

Deborah A. Zarin, M.D., Tony Tse, Ph.D., Rebecca J. Williams, Pharm.D., M.P.H.,
and Sarah Carr, B.A.

Title VIII of the Food and Drug Administration (FDA) Amendments Act of 2007 (FDAAA) expanded the legal mandate for sponsors and others responsible for certain clinical trials of FDA-regulated drug, biologic, and device products to register their studies and report summary results information to ClinicalTrials.gov,¹ which is managed by the National Library of Medicine at the National Institutes of Health (NIH). The statute expanded registration requirements and provided a legally defined timeline with specific requirements for the systematic reporting of summary trial results. Although statutory components took effect before 2010, the FDAAA directed the Department of Health and Human Services (HHS) to issue regulations regarding certain statutory provisions and to consider possible expansion of the requirements through rule-making.

developed the final rule, which was made publicly available on September 16, 2016. Simultaneously, the NIH issued a complementary final policy, under which NIH-funded awardees and investigators will be expected to submit registration and results information for all NIH-funded clinical trials, whether or not the trials are covered by the FDAAA requirements.⁶

Here, we summarize and highlight key points about the final rule (see box).

BACKGROUND

The FDAAA established legal requirements for sponsors and designated principal investigators (i.e., responsible parties) to report specified clinical trial information for certain applicable clinical trials to ClinicalTrials.gov. In addition to registration, the statute established a system and man-

Acknowledgments

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- Becky Williams



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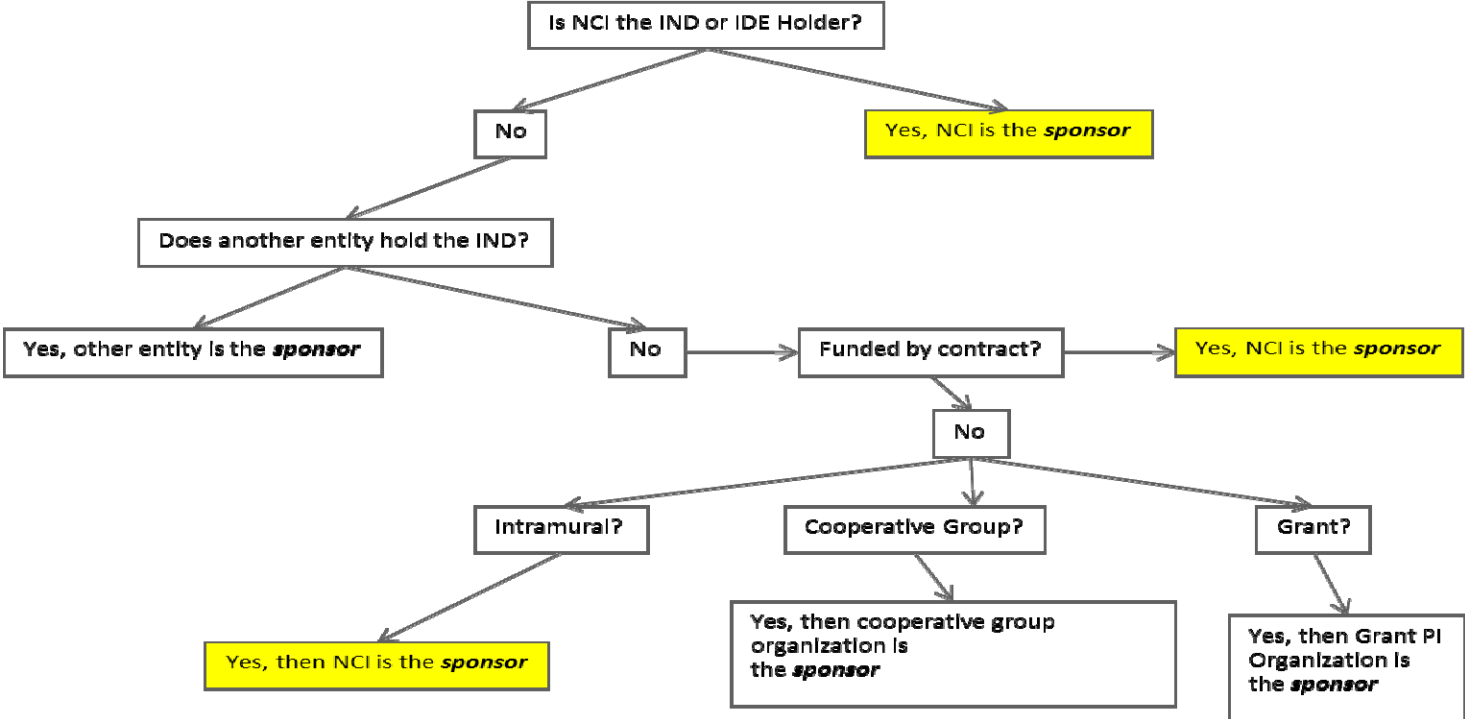
Clinical Trial – NIH Definition

A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

Primary Completion Date

The date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.

NCI: Who is the Trial Sponsor (per FDAAA)?





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