



# Yale Center for Clinical Investigation

ClinicalTrials.Gov  
and the  
FDA Amendments Act of 2007,  
P.L. 110-85, (Section 801)

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## Acknowledgements

- McCray, Alexa, T., Better Access to Information About Clinical Trials, *Annals of Internal Medicine*, 17 Oct 2000, Vol. 133, Number 8, 609-614.
- Mark Barnes, FDA Amendments Act of 2007 (PL 110-85): Mandatory Registering of Clinical Trials and Reporting of Results, FDA News Audio conference, 28 Nov 2007.
- Williams, Erin, D., Clinical Trials Reporting and Publication, Congressional Research Service Report, 12 July 2007, Order Code RL32832.
- Zarin, Deborah, A., Expansion of ClinicalTrials.gov: Public Law 110-85, Section 801, Public Responsibility in Medicine and Research Annual Convention, Boston, MA, 3 Dec 2007.
- Guidance on New Law (Public Law 110—85) Enacted to Expand the Scope of ClinicalTrials.gov:Registration. Notice # NOT-OD-08-014.
- Department of Health and Human Services, Food and Drug Administration, Guidance for Industry, Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions, 2002.
- Uscinski, Kathleen, An Update on Clinical Trial Registries, Public Responsibility in Medicine and Research Annual Convention, Boston, MA, 3 Dec 2007.



## Overview

- Introduction
  - Background
  - Requirements
  - Terms
  - ClinicalTrials.Gov Demonstration
- Resource Material Package Attached



## Introduction

- ClinicalTrials.gov
  - Web-based open-access clinical trial database repository containing information about active and closed clinical trials
  - NIH managed through the National Laboratory of Medicine
  - Federal Modernization Act of 1997, P.L. 105 – 115, (FDAMA) established clinicaltrial.gov (active 2000); reporting of drug trials involving serious and life threatening diseases or conditions, Group C cancers, and expanded use
  - FDA Amendments Act of 2007, P.L. 110-85, (Section 801), established mandatory reporting of applicable clinical trials involving drugs, biologics, and devices plus (in the future) reporting of results (possibly including serious or frequent adverse events)
    - Effective prior to implementing regulation (Code of Federal Regulation [CFR])



## Background

- Many Different Influences/Forces, such as:
  - Evidence-based medicine improves medical practice (clinical trial as ‘Gold Standard’)
  - FOIA – Public monies – NIH regulations issued pursuant to 1999 P.L. 105-277 (limited to published findings produced under an award used to develop federal agency action)
  - Reduce publication bias (non-completed/negative or inconclusive results unpublished)
  - Ensure publications reflect original purposes and designs
  - More widely disseminate enrollment opportunities
  - Stakeholder Advocacy Groups (e.g., AIDS, cancer)
  - ICMJE Policies – 2004, 2005, plus 2007 revision
  - Pharma, 2004; AMA, 2004; IOM 2006; AAMC, 2006; WHO, 2007
  - State initiatives (e.g., Maine)
  - Abuses - Olivieri/U of Toronto (“No right to publish”), “Selective publications” allegations Re: SSRIs and Celebrex
  - Emerging Medical Biotechnology – New Possibilities
  - Mainstreaming of Internet & Other Technological Innovations
  - 2002 FDA study found that only 48% of Group C cancer protocols were registered
  - 2005 FDA study found that 67% of companies required to register studies had done so
  - Mechanism to track progress of clinical trials (FDA)



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## Requirements Section 801

- Register on-going applicable Phase II-IV drugs, biologics, and device trials for all diseases and conditions (**by later of 26 Dec 07 or 21 days after first subject is enrolled**)
- **Applicable Drug/Biologic Trial:** Controlled clinical investigation; *Clinical investigation* means any experiment in which a drug/biologic is administered or dispensed to, or used, involving one or more human subjects
- **Applicable Device Trial:** Prospective clinical study of health outcomes comparing an intervention with a device subject to 510(k), 515, or 520(m), against a control in human subjects (other than a small clinical trial to determine the feasibility of a device where the primary outcome measure relates to feasibility and not to health); Additionally, post-marketing pediatric device trials.



## Requirements Section 801

- 12 previously optional data fields now required (by 26 Dec 2007)
- 4 new data elements added (by 26 Dec 2007)
- Links to FDA advisory committees, public health advisories, Medline citations
- Penalties for non-compliance (can be up to \$10k per day, denial or withholding of federal funds)

If you intend to publish – Remember **ICMJE** Policy Plus be  
Aware of Policies of Other Journals



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## Requirements Section 801

- **Exceptions**

- Trials on-going as of 27 Sept 2007 that do NOT involve a serious or life-threatening disease or condition (SLT): 27 Sept 2008 **(1)**
- Trials completed prior to 27 Sept 2007 **(2)**
- SLT trials completed prior to 26 Dec 2007 **(3)**
- Devices not yet approved or cleared – “Lock Box” - still have to register but will not be publicly available until device cleared or approved

**(1) Recommend Register Now**

(2) Would be useful for archival purposes but too burdensome

(3) Drug trials should have been registered per FDAMA



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## Requirements Section 801

- Information may not be false or misleading
- **Updating of information** required at **least every 12 months**, with dates of change indicated
- **Updating required within 30 days of recruitment status changes or completion of trial**
- Certification that registration has been accomplished required in progress report for all grants from any agency of DHHS, including FDA, NIH, or Agency for Healthcare Research and Quality
- NIH Secretary is required to update regulations to require that a statement be added to the informed consent form (ICF) that the clinical trial has been or will be added to the registry (Recommend no action at this time unless otherwise directed by funding program office or sponsor or a Yale IRB)



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## ICMJE Policy for Publication

- Phase I trials included (at this time; trials with enrollment on or after July 2008)
- Any research study that prospectively assigns human participants to one or more health-related interventions to evaluate the effects on health outcomes
  - Health-related interventions include any intervention used to modify a biomedical or health-related outcome; e.g., drugs, surgical procedures, devices, behavioral treatments, dietary interventions
  - Note: Journals not part of ICMJE may have different policies; Policies may change



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## Terms

- **Responsible Party**: the sponsor or the PI if so designated by a sponsor, so long as the PI is responsible for conducting the trial, has access to and control over the data from the trial, has the right to publish the results of the trial, and has the ability to meet all requirements for submitting trial information to ClinicalTrials.gov (**Sponsor** = initiates the clinical investigation, but does not actually conduct the investigation; typically – pharmaceutical, biotech, or device manufacturer sponsoring the trial is the responsible party).

### **If the PI holds the IND/IDE – responsible for registering the trial (Investigator-Sponsor)**

- **Other Protocols Operating Under the Investigator-Sponsor's IND/IDE**
  - Coordinate with the Holder to ensure registration
- **Investigator-Initiated trials without an IND/IDE** – the PI is most likely responsible for registering the trial
- **PIs are responsible for determining whether he/she is the responsible party and that applicable trials are appropriately registered**



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## Terms

- NIH Funded/Supported Trials:
  - If the NIH holds the IND/IDE, most likely NIH will be the responsible party
  - Where there is no IND/IDE, or when NIH does not hold the IND/IDE, most likely the funding recipient is the responsible party
  - Check with your NIH point of contact to clarify who is the responsible party and/or what is expected
    - ClinicalTrials.gov will provide specific agency/program office registration point of contact for inquires when supplied with award #
  - NIH encourages registration of ALL trials whether required under Section 801 or not



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## Terms

- Completion Date = the date that the final subject was examined or received an intervention for the purposes of final collection of the primary outcome, whether the trial concluded or was terminated.
- On-Going = 1 or more subjects enrolled and the date is before the completion date.
- Serious or life-threatening disease or condition:
  - Life threatening or serious disease or conditions: (1) Diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted; and (2) diseases or conditions with potentially fatal outcomes, where the endpoint of a clinical trial is survival.



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- ClinicalTrials.Gov Demonstration
  - Overall Procedure
  - Examples of Data Fields
  - Data Entry Conventions
  - Demonstration
    - Initial Submission
    - Updates
    - Edits
- Listing of Yale (YCCI) ClinicalTrials.Gov Protocol Registration System Administrators



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## Overall Procedure

- Protocol Registration System (PRS) organized by organizational accounts
- Organizational account (Yale) held by Yale Center for Clinical Investigation (YCCI)
- Provide YCCI PRS Administrator with name and e-mail of responsible party; YCCI sets up user account with PRS
- User receives user account and PW from PRS
- Sign onto PRS, enter data, record(s) goes to YCCI PRS Administrator
- YCCI PRS Administrator reviews and approves record(s); releases to ClinicalTrials.Gov
- ClinicalTrials.Gov automated and manual review; posted publicly shortly thereafter
  
- Yale Cancer Center trials registered by Maria Mezes, 737.1596; Contact her if you have a Yale Cancer Center trial



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## Data Fields

- Examples
  - Brief Title (layperson's language)
  - Brief Summary (layperson's language)
  - Primary Purpose
  - Study Design
  - Primary disease or condition (MeSH language)
  - Intervention name and type
  - Study start and expected (actual) completion date
  - Primary & Secondary Outcomes
  - Target # of subjects
  - Name of sponsor, responsible party
  - Facility name and location, plus contact information
- Drop Down Menu for many fields



## Suggested Data Entry Conventions

- Consistent terms (e.g., Yale University School of Medicine, rather than Yale or Yale School of Medicine)
- Medical Subject Headings (MeSH) descriptors for disease or condition (<http://www.nlm.nih.gov/mesh>)
- If more than one study coordinator for one PI with multiple studies, use PI's user ID and PW for all
- Use IRB # (HIC, Nursing, FAS) for Organization's Unique Protocol ID
- Use grant/sponsor unique identifier for secondary IDs
- Complete optional data fields as appropriate, e.g., acronym for study –
- “ENABLE 1”
- Register after IRB approval



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## Yale (YCCI) PRS Administrators

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- Resource Material (hand out)
  - Guidance on New Law (Public Law 110-85) Enacted to Expand the Scope of ClinicalTrials.Gov: Registration (NIH)
  - What's New in the ClinicalTrials.Gov Protocol Registration System (NIH Laboratory of Medicine)
  - ClinicalTrials.Gov Fact Sheet; Registration at ClinicalTrials.Gov: As required by Public Law 110-85 (NIH Laboratory of Medicine)
  - Quick Start Guide, Protocol Registration System (NIH Laboratory of Medicine)
  - **ClinicalTrials.Gov Data Element Definitions** (NIH Laboratory of Medicine)
  - Clinical Trial Registration - Looking Back and Moving Ahead, ICMJE, JAMA, 4 June 2007



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## Demonstration (Not Available This Web Version)

- **ClinicalTrials.Gov**
  - Initial Submission
  - Updates
  - Edits