Clinicaltrials.gov - ramped up: Registering, reporting, notifying in informed consent form

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What is ClinicalTrials.gov

- **A clinical trials registry and results database** that:

  (1) Was developed by the National Institutes of Health through the National Library of Medicine in collaboration with the Food and Drug Administration as a result of the Food and Drug Administration and Modernization Act of 1997 (FDAMA).

  (2) Provides public access to information about clinical trials conducted in the United States and internationally regardless of funding source (internal, federal, industry, private)

  Additional background information can be found at the ClinicalTrials.gov. Click on "Read More" and Guidance for Industry

www.clinicaltrials.gov

Registration Background

- In 2000, the clinicaltrials.gov registry predominately contained information about NIH funded studies. Guidance for industry was made available for registration of investigational drugs for treatment of serious or life-threatening disease. Mandatory data elements were established as reporting thresholds to ensure consistency. Studies were required to be registered no later than 21 days after the trial was open for enrollment.

- In 2005, as a prerequisite for publication in their journals, the International Committee of Medical Journal Editors (ICMJE) instituted the requirement that all clinical trials beginning on or after July 1, 2005 be registered **prior to enrollment of the first patient**. In 2008, the ICMJE expanded the requirement to cover Phase I studies.

- VCU adopted the registration philosophy of the ICMJE as contained in the **Clinical Trials Protocol Registration** policy/guideline which can be found at:

http://www.research.vcu.edu/p_and_g/clinicaltrials.htm

Home - ClinicalTrials.gov

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

ClinicalTrials.gov is a registry and results database of federally and privately supported clinical trials conducted in the United States and around the world. ClinicalTrials.gov gives you information about a trial's purpose, who may participate, locations, and phone numbers for more details. This information should be used in conjunction with advice from health care professionals. **Read more...**

Search for Clinical Trials

Find trials for a specific medical condition or other criteria in the ClinicalTrials.gov registry. ClinicalTrials.gov currently has 121,252 trials with locations in 179 countries.

Investigator Instructions

Get instructions for clinical trial investigators/sponsors about how to register trials in ClinicalTrials.gov. Learn about mandatory registration and results reporting requirements and US Public Law 110-85 (FDAAA).

Background Information

Learn about clinical trials and how to use ClinicalTrials.gov, or access other consumer health information from the US National Institutes of Health.

Resources:

- Understanding Clinical Trials
- What's New
- Glossary

Study Topics:

- List studies by Condition
- List studies by Drug Intervention
- List studies by Sponsor
- List studies by Location

Current Registration Requirements Federal Law

- On September 27, 2007, The Food and Drug Administration Amendments Act of 2007 (FDAAA) was passed which expanded the types of clinical trials required to be registered and included a requirement for the submission of results.
- Under Title VIII of FDAAA (Public Law 110-85) **Applicable Clinical Trials** are required to be registered at ClinicalTrials.gov and results reported by the **Responsible Party.** http://www.gpo.gov/fdsys/pkg/PLAW-110publ85/pdf/PLAW-110publ85.pdf
- NIH Fact sheet - good source of information for registration questions. Includes information about timing and definitions of Responsible Party and Applicable Clinical Trial.

http://prsinfo.clinicaltrials.gov/s801-fact-sheet.pdf

Who is the Responsible Party?

- US Public Law 110-85, Title VIII, Section 801, defines the term "**responsible party,**" with respect to registering and reporting results for a clinical trial, as follows:
  - "the sponsor of the clinical trial (as defined in 21 CFR 50.3) or
  - the principal investigator of such clinical trial if so designated by a sponsor, grantee, contractor, or awardee, so long as the principal investigator is responsible for conducting the trial, has access to and control over the data from the clinical trial, has the right to publish the results of the trial, and has the ability to meet all of the requirements for the submission of clinical trial information."

- VCU generally has responsibility for registration of investigator initiated studies regardless of funding source (NIH, industry funded, internally funded).

http://prsinfo.clinicaltrials.gov/definitions.html

What is an "Applicable Clinical trial" and how do I know if my trial is an "Applicable Clinical Trial?"

"Applicable clinical trials" generally include:

Controlled interventional studies (with one or more arms) of drugs, biological products, or devices that are subject to FDA regulation:

- the trial has one or more sites in the United States,
- involves a drug, biologic, or device that is manufactured in the United States (or its territories), or
- is conducted under an investigational new drug application (IND) or investigational device exemption (IDE).

Does not include Phase 1 Studies.

Trial sponsors and investigators (not the IRB) have the responsibility of determining whether or not a trial is an "applicable clinical trial."

- "Applicable clinical **device trial" if:**

  (I) the trial prospectively compares a device-based intervention subject to FDA regulation against a control in human subjects; or

  (II) the trial is a pediatric post-market surveillance trial. 42 U.S.C. § 282(j)(1)(A)(ii).

- "Applicable clinical **drug trial" if:**

  (1) the trial is a controlled clinical investigation, other than a phase I clinical investigation, of a drug subject to FDA regulation. 42 U.S.C. § 282(j)(1)(A)(iii)(I

http://grants.nih.gov/ClinicalTrials_fdaaa/index.htm

More about Determining an "Applicable Clinical Trial"

- National Institutes of Health/National Library of Medicine(NIH/NLM) has been given the statutory authority to interpret the definition of an "Applicable Clinical Trial". The current interpretation by NIH/NLM can be found in PDF form at the following site: http://prsinfo.clinicaltrials.gov/ElaborationsOnDefinitions.pdf
- A flowchart to aid in determining an "Applicable Clinical Trial" can be found as a PDF file here. Applicability can also be determined by answering questions as prompted at the following website.

  http://grants.nih.gov/clinicaltrials_fdaaa/ACTs_under_FDAAA.htm

Registration Timelines and VCU Requirements

- In accordance with Title VIII under FDAAA, studies meeting the definition of an "**Applicable Clinical Trial**" must be registered no later than 21 days after enrollment of the first patient.

HOWEVER

- In accordance with VCU's Clinical Trials Protocol Registration guideline, all studies meeting the definition of a **clinical trial (any research study that prospectively assigns human participants or groups of humans to one or more health-related intervention to evaluate the effects on health outcomes)** must be registered prior to enrollment of the first subject. **This is the definition adopted by the World Health Organization and is supported by the International Committee of Medical Journal Editors (ICMJE). It includes Phase I studies.**

AND

- "The NIH encourages registration and results reporting for **all NIH-supported clinical trials**, regardless of whether or not they are subject to FDAAA." http://grants.nih.gov/ClinicalTrials_fdaaa/index.htm

Federal Law vs. VCU Requirement. Why the distinction?

- VCU **supports** the registration of all **clinical trials prior to enrollment of the first subject** as a mechanism to ensure publication of results (whether positive or negative) in appropriate journals. VCU has been registering studies on clinicaltrials.gov since 2005.
- The 2007 Federal Law **mandates** that all **Applicable Clinical Trials** be **registered no later than 21 days after enrollment of first subject and results reported no later than one year after the Primary Completion Date** (defined as "the date the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome". This is required whether the study was completed or was terminated.

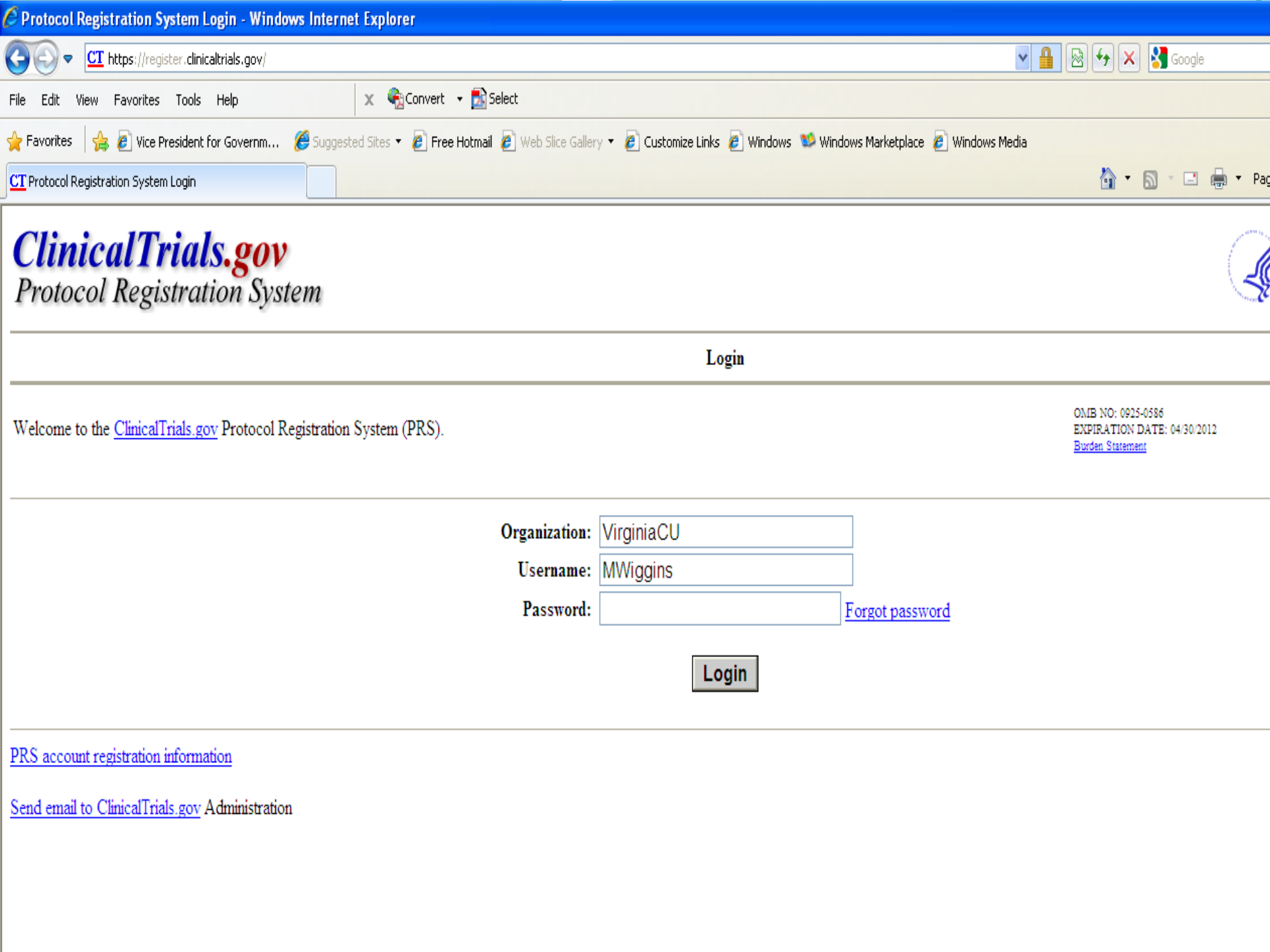
Are there Consequences for not (or late) Registering/Reporting Results?

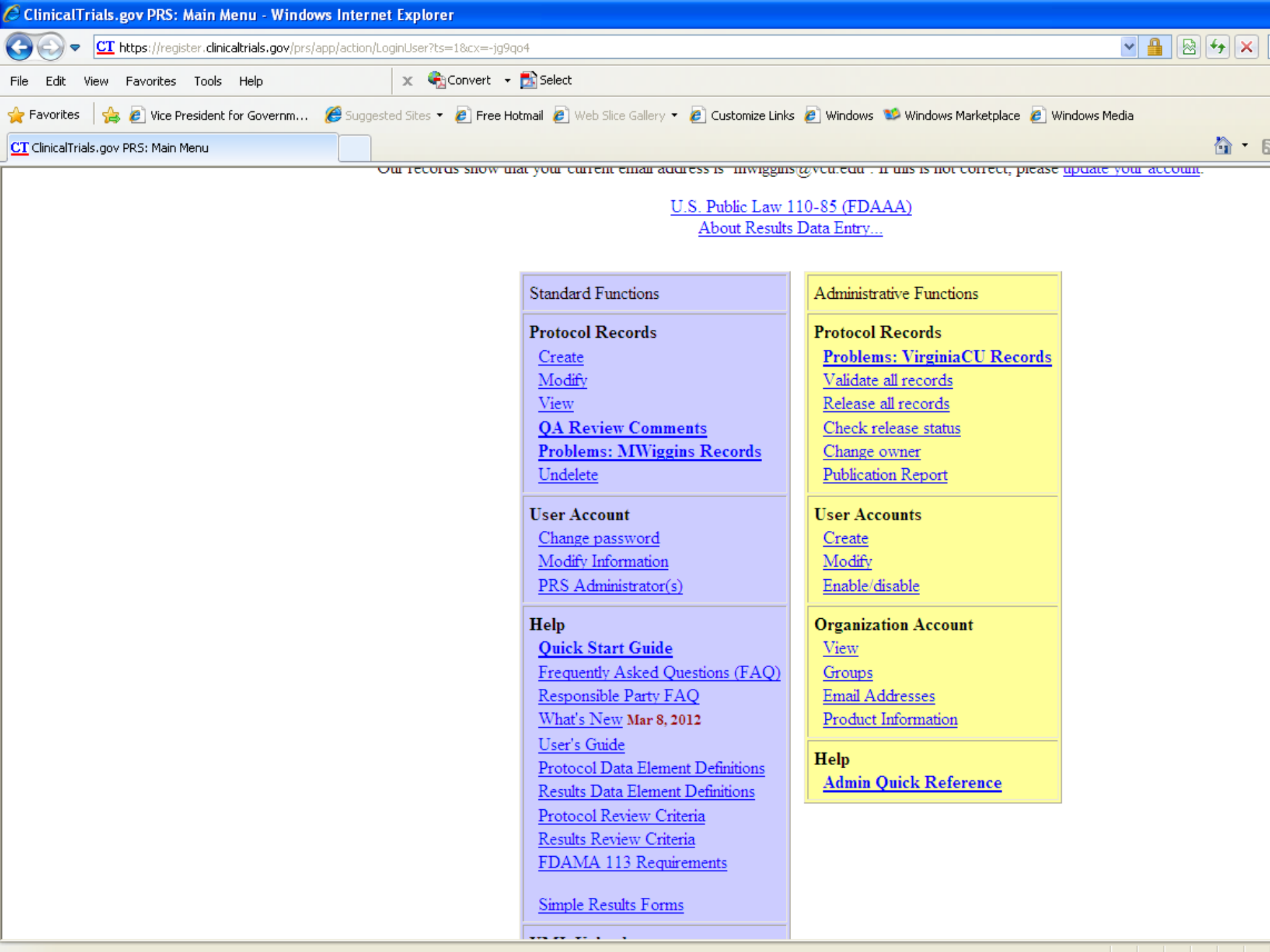
YES, several possible, including:

- Notifications of noncompliance
- Civil monetary penalties of up to **$10,000 per day**.
- NIH requires certification of compliance (NCT number) in competing grant applications and progress reports for existing grants funded in whole or in part by NIH. Non compliance may cause a loss of future funding or disallowance of current funding.

What are the Registration Steps?

- Notify Melanie Wiggins, the VCU Administrator for ClincialTrials.gov at mwiggins@vcu.edu to request account set up. Account information will be emailed.
- Registration will be accomplished through the following site: https://register.clinicaltrials.gov
- Menu-driven Protocol Registration System


Protocol Registration System Login - Windows Internet Explorer
https://register.clinicaltrials.gov/
File Edit View Favorites Tools Help
Convert
Select
Favorites
Vice President for Governm...
Suggested Sites
Free Hotmail
Web Slice Gallery
Customize Links
Windows
Windows Marketplace
Windows Media
Protocol Registration System Login
ClinicalTrials.gov
Protocol Registration System
Login
Welcome to the ClinicalTrials.gov Protocol Registration System (PRS).
OMB NO: 0925-0586
EXPIRATION DATE: 04/30/2012
Burden Statement
Organization: VirginiaCU
Username: MWiggins
Password:
Forgot password
Login
PRS account registration information
Send email to ClinicalTrials.gov Administration


ClinicalTrials.gov PRS: Main Menu - Windows Internet Explorer
https://register.clinicaltrials.gov/prs/app/action/LoginUser?ts=1&cx=-jg9qo4
File Edit View Favorites Tools Help
Convert
Select
Favorites
Vice President for Governm...
Suggested Sites
Free Hotmail
Web Slice Gallery
Customize Links
Windows
Windows Marketplace
Windows Media
ClinicalTrials.gov PRS: Main Menu
Our records show that your current email address is "mwiggins@vcu.edu". If this is not correct, please update your account.
U.S. Public Law 110-85 (FDAAA)
About Results Data Entry...
Standard Functions
Protocol Records
Create
Modify
View
QA Review Comments
Problems: MWiggins Records
Undelete
User Account
Change password
Modify Information
PRS Administrator(s)
Help
Quick Start Guide
Frequently Asked Questions (FAQ)
Responsible Party FAQ
What's New Mar 8, 2012
User's Guide
Protocol Data Element Definitions
Results Data Element Definitions
Protocol Review Criteria
Results Review Criteria
FDAMA 113 Requirements
Simple Results Forms
Administrative Functions
Protocol Records
Problems: VirginiaCU Records
Validate all records
Release all records
Check release status
Change owner
Publication Report
User Accounts
Create
Modify
Enable/disable
Organization Account
View
Groups
Email Addresses
Product Information
Help
Admin Quick Reference

ClinicalTrials.gov
Protocol Registration System

Send message to PRS

Create New Protocol Record

To avoid duplicate or invalid registration of your study, check the following before proceeding with registration:

1. **Section 801 studies may only be registered by the Responsible Party.** If this is an applicable clinical trial as defined by US Public Law 110-85, Title VIII, Section 801, ensure that your organization is the Responsible Party as defined by the law before registering the study.
2. **IND/IDE studies may only be registered by the IND/IDE holder.** If the study is subject to US Food and Drug Administration regulations, under an Investigational New Drug (IND) Application or Investigational Device Exemption (IDE), ensure that your organization is the IND/IDE holder before registering the study.
3. **For NIH-funded studies, coordinate with the relevant Institute or Center.** If this is a US National Institutes of Health (NIH) funded study, registration should be coordinated with the sponsoring NIH Institute or Center to avoid duplicate registration.
4. **Multi-site studies are NOT registered by individual sites.** If this is a multi-site study it must be registered only once, by the sponsor (primary organization that oversees implementation of study and is responsible for data analysis) or its designated principal investigator (PI).
5. **Coordinate with all collaborators before registering.** If the study has multiple collaborators, contact the other organizations to confirm that the study has not already been registered and to notify them that your organization, as sponsor or its designated PI, is registering the study.
6. **Refer to the ClinicalTrials.gov Review of Protocol Submissions document** for a description of items evaluated by ClinicalTrials.gov after protocol information is submitted.

Unique Protocol ID: *

Brief Title: *

Continue Cancel

* Required by ClinicalTrials.gov

Can Posting of Information be Delayed?

Following information obtained from registration website as noted below:

Delayed Posting? **(FDAAA)**
Definition: If this is a Section 801 applicable clinical trial, indicate whether this trial includes a **device** NOT previously approved or cleared by the US FDA for any use, as specified in US Public Law 110-85, Title VIII, Section 801. Select Yes/No. If "Yes" is selected, full posting of the trial information on ClinicalTrials.gov will be delayed until after the device has been approved or cleared. **At that time, it is the registrant's responsibility to change this selection to "No" and release the record for full publication.**

https://register.clinicaltrials.gov/prs/html/definitions.html#delayedPosting

Results Reporting

Presentations containing general information about results reporting can be found at http://prsinfo.clinicaltrials.gov/

- Results: Participant Flow Module
- Results: Baseline Characteristics Module
- Results: Outcome Measures and Statistical Analyses Module
- Results: Adverse Events Module

Description of Data Elements Definitions

- http://prsinfo.clinicaltrials.gov/results_definitions.html

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Send message to PRS

About Results Data Entry

This guide provides a quick introduction to adding clinical study results information to a protocol record that has been registered on ClinicalTrials.gov. For background information, refer to the PRS Information Site's PRS and U.S. Public Law 110-85.

1. **Review and update the protocol record as needed** - pay special attention to arms (groups) and outcome measures, including time frame, as they are used to prefill the results section.
2. **Create the results section** - from the Edit Protocol screen, click on the Enter Results link. The Pre-fill Results from Protocol screen appears, showing the information to be inserted into the results section. If the information is correct, click OK. If not, click Cancel and make the necessary corrections in the protocol section.
3. **Fill in results section** - after results creation the Results Overview screen appears. Use the Edit links to the left to fill in the results section. Refer to the Results Data Element Definitions (accessible either from the Main Menu or results editing screens) for explanations of each field or option menu in the results editing screens. Messages (ERROR, WARNING, ALERT, INFO) on the results screens help in identifying missing or inconsistent content, as in the protocol section.
4. **Maintain combined protocol/results record** - use the Edit Protocol link near the top of the Results Overview screen to return to the Edit Protocol screen. A summary of the results information is now shown, along with any associated errors, warnings or informational messages. The Edit link beside the results summary leads back to the Results Overview screen.

   From this point, all actions (e.g., Complete, Release) apply to the combined protocol/results record. After a record is released with results for the first time the Initial Results Release Date is shown in the status area of the Edit Protocol screen. The Preview screen includes a rough approximation of how the results information will appear on ClinicalTrials.gov.

XML Upload - The protocol record Document Type Definition now includes a tag for records with results. The content (subordinate tags and data) of the result tag is documented in the Results XML Schema, accessible from the Main Menu. Sponsors wishing to submit results via XML upload should first enter results using the PRS web interface to gain familiarity with the results data elements and validation rules. Downloading XML for complete, valid records containing results will then provide useful examples.

Close

Can Results Reporting be Delayed?

- **Yes, but only in very specific cases such as indicated on the clinicaltrials.gov website listed below:**

  "42 U.S.C. 282(j)(3)(E)(iii)-(v) allows for delayed submission of results information with certification.* A responsible party may submit a certification for delayed submission of results information for an **applicable clinical trial that is:**
- **completed before the drug or device is initially approved, licensed, or cleared by the FDA ("seeking initial approval") or**
- **studying a new use of an FDA-approved drug or device (i.e., a use not included in the labeling) for which the manufacturer of a drug or device is the sponsor of the trial and has filed or will file within a year an application to the FDA for approval or clearance of that use ("seeking approval for a new use")** "

- http://prsinfo.clinicaltrials.gov/DelayedSubmission.html

What study-specific information is entered into ClinicalTrials.gov?

Summaries of Clinical Study Protocols:

- summary of the purpose of the study
- recruiting status
- disease or condition and medical product under study
- research study design
- phase of the trial
- criteria for participation
- location of the trial and contact information

Summaries of Clinical Study Results for some studies:

- description of study participants (e.g., number enrolled, demographic data)
- overall outcomes of the study
- summary of adverse events experienced by participants

IRB Review of ClinicalTrials.gov entries is NOT Required

Clinical trial websites that **provide *only* directory listings with basic descriptive information about clinical trials in general (as listed above) do not need to be reviewed by an IRB.** Examples of clinical trial listing services that do not need IRB review and approval include the National Institutes of Health (NIH) **ClinicalTrials.gov website**, the NIH National Cancer Institute's cancer clinical trials listing (Physician Data Query [PDQ]), and the government-sponsored AIDS Clinical Trials Information Service (ACTIS).

Office for Human Research Protections (OHRP)
Guidance on Institutional Review Board Review of Clinical Trial Websites
Date: September 20, 2005

http://www.hhs.gov/ohrp/policy/clinicaltrials.html

New required basic element of Informed Consent (for applicable CTs)

Purpose: Inform potential participants in the informed consent form when a description of their applicable clinical trial must be available on the Web at ClinicalTrials.gov

What: Information about applicable clinical trials has been or will be, entered into a databank which is publicly accessible at http://www.ClinicalTrials.gov

Where: 21CFR 50.25(c)

Dates

- **Effective date:** March 7, 2011

- **Enforcement/compliance date:**

  March 7, 2012 for all IC documents and processes related to an applicable clinical trial that is initiated on or after the compliance date

Required language in Informed Consent

" A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."

FDA Guidance Document

Questions and Answers on Informed Consent Elements,

21 CFR § 50.25(c)

U.S. Department of Health and Human Services

Food and Drug Administration

Office of Policy and Office of Good Clinical Practice

Office of the Commissioner

February 2012

http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM291085.pdf?source=govdelivery

11. Will re-consent be required for ongoing trials after March 7, 2012?

No, if the applicable clinical trial was initiated before March 7, 2012, then these informed consent documents do not have to be in compliance with the new requirement. Subjects who consent to an applicable clinical trial via documents approved before March 7, 2012, will not need to be re-consented based solely on the new regulations.

Even if sponsors or investigators revise consent documents for other reasons, as long as the documents were initially approved before March 7, 2012, the revised consent forms do not have to include the statement.

13. What are the responsibilities of an IRB under the new rule?

IRBs continue to have the responsibility to review and approve informed consent documents. 21 CFR § 56.109(b). The waivers to documentation of informed consent regarding certain studies still apply. 21 CFR § 56.109(c)(1). **Even if documentation is waived under 21 CFR § 56.109(c)(1), the trial participant still provides consent and the statement is required during the oral presentation of the research and/or in the written statement regarding the research**, if required by the IRB under 21 CFR § 56.109(d). Under 21 CFR §§ 50.23 and 50.24 regarding exceptions to informed consent, the statement is also required in the informed consent documents if these trials are applicable clinical trials.

In VCU Biomedical Consent template:

CONFIDENTIALITY

Potentially identifiable information about you will consist of *[List e.g., tissue samples, surveys, interview notes and recordings, audiotapes of consultations and interviews, and data abstracted from the medical record]*. Data is being collected only for research purposes. *[Note how the data will be identified, stored and protected]. Etc, etc, etc*

You should know that research data or (medical information if applicable) about you may be reviewed or copied by the sponsor of the research or by Virginia Commonwealth University. Personal information about you might be shared with or copied by authorized officials of the Federal Food and Drug Administration, or the Department of Health and Human Services (if applicable).

[Include this language (required by the FDA) if this study is a clinical trial]

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Website will include a summary of the results. You can search this Web site at anytime.

17. Does the new statement have to be included in informed consent documents for trials with de-identified data—
that is, trials that are not subject to the Health Information Portability and Accountability Act (HIPAA)?

- If the trial is determined to be an applicable clinical trial, the investigator or sponsor must comply with the new regulation regardless of any determinations concerning HIPAA requirements.