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Knowledge that will change your world

New ClinicalTrials.gov Requirements: *How it Impacts your Research*

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Objectives

- History of Clinical Trials.gov
- What are the changes?
- How can we accomplish this?

History:

- 1997: law mandating registration of trials of investigational new drugs for serious or life-threatening diseases

- 2000: implementation of ClinicalTrials.gov – publicly accessible online database operated by the National Library of Medicine
  - International efforts followed:
    - International Committee of Medical Journal Editors

History (con‘t):

- 2007: requirement for results reporting: FDAAA

- 2016: the Final Rule is no longer a statute; as a Final Rule has more impact and more weight

Released Sept 16,2016 – new requirements

- Goal – expand transparency; clarify language, and enhance compliance

- Two new sets of requirements:
  - Dept of Health and Human Services (DHHS) – Notice of Final Rule
    - Effective Jan 18, 2017
    - The Final Rule is no longer a statute; as a Final Rule has more impact and weight
  - NIH - NOT-OD-16-149
    - New NIH policy supporting the Notice of Final Rule and expanding requirements for NIH funded studies

DHHS requirements: ClinicalTrials.gov reporting

Clarifies the statutory language

- Provides objective, structured criteria for evaluating whether a study is an “applicable clinical trial” (ACT). Clarifies that for purposes of the final rule, all multi-group studies and all single-group interventional studies with pre-specified outcome measures are considered “controlled”
- Clarifies distinction between “secondary” and other pre-specified outcome measures

Expands transparency beyond the basic statutory (initial) requirements

- Requires submission of baseline information on race or ethnic group, *if collected* during the clinical trial, and other characteristics associated with primary outcome measures
- Defines required levels of specification for outcome measures
- Requires submission of information about adverse-event timeframe and collection method, as well as all-cause mortality
- Requires submission of full protocol and statistical analysis plan (if not in protocol) at the same time as submission of results information
- Provides a list of potential legal consequences for non-compliance.

Other issues

- *Records will be posted within a specified time frame, may be posted without complete review by ClinicalTrials.gov with a disclaimer as to accuracy*

NIH requirements: ClinicalTrials.gov reporting

- All protocols supported in total or in part by NIH must be posted

- Penalties: lack of compliance could result in PI and or institution being unable to obtain future funding from the NIH

Which protocols are required to be registered and have results reported?

- Per the FDAAA
  - Trials of drugs and biologics: Controlled clinical investigations, other than phase 1 clinical investigations, of drugs or biological products subject to Food and Drug Administration (FDA) regulation
  - Trials of devices: 1) Controlled trials with health outcomes of devices subject to FDA regulation, other than small feasibility studies, and 2) pediatric post market surveillance required by FDA
- Per the NIH
  - The policy applies to all NIH-funded awardees and investigators conducting clinical trials funded in whole or in part by the NIH regardless of study phase, type of intervention, or whether they are subject to the statute and to the rule. (including phase I)
- Per Medicare
  - NCT# required if there are clinical billables [currently no requirement for results reporting]
- Journals
  - Journals may ask for NCT# (may not know this until end of study)

Two primary components

- Registration
  - Q 12 month updates
  - Realtime updates

- Results reporting
  - Within 12 months after last subject meets the primary outcome measure

When should registration be completed?

- Per the FDAAA
  - Within 21 days of first subject enrolled
- Per the NIH
  - Within 21 days of first subject enrolled
- *Given that* the information about being registered on ClinicalTrials.gov will be in consent forms
  - Prior to enrolling first subject
- *Given that* clinical billables will require registration prior to payment
  - Prior to enrolling first subject

When are results reported?

- Per the FDAAA
  - Within 12 months after the last subject has met his/her primary outcome measure
- Per the NIH
  - Within 12 months after all subjects have met his/her primary outcome measure

- Exceptions:
  - If reporting results on ClinicalTrials.gov creates risk to the study outcomes, PI can petition for a delay

Penalties are enforced when there is failure to comply with the Final Rule and, when applicable, the NIH policy. What is compliance?

- Registering within the required time windows
- Reporting results within required time frame
- Responding to Review Comments in a windows
  - 15 Days for registration and registration updates
  - 25 Days for results updates

EXTENSION REQUEST

The Director of the National Institutes of Health (NIH) may extend the deadline for submission of results information for an Applicable Clinical Trial if the Responsible Party submits a written request that demonstrates good cause for the extension and provides an estimate of the date on which the results information will be submitted. Pending publication is not considered good cause for an extension.

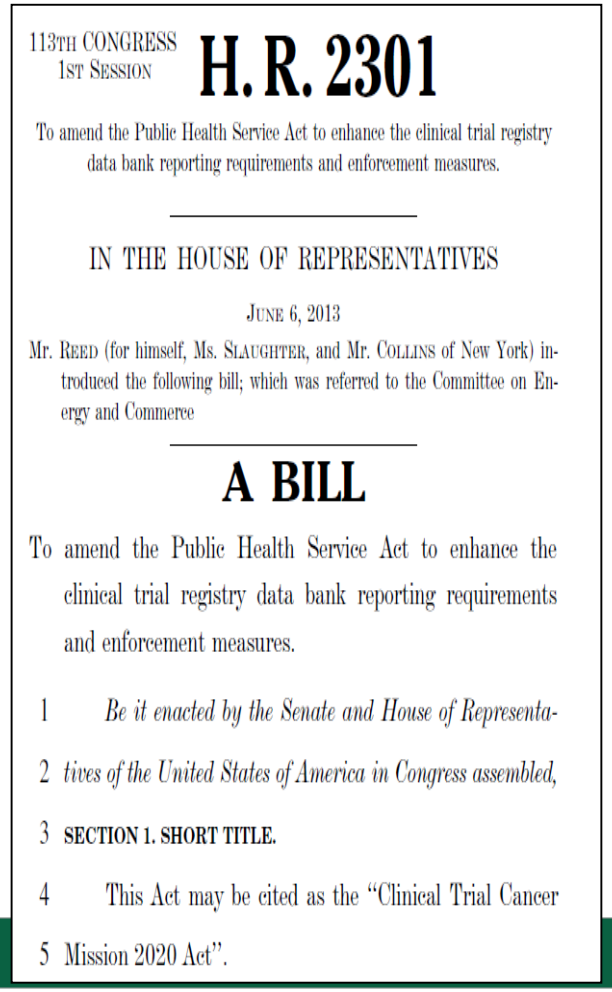
Submitting a Certification or Request for Extension for Delayed Submission of Results

- A certification or request for extension is submitted via the Protocol Registration and Results System (PRS). A trial must have a ClinicalTrials.gov Identifier (NCT Number) prior to submission of a certification or request for extension. Submission of this certification will facilitate automated identification of trials that are not yet required to submit results.

And the penalties

- Per the FDAAA (not new, but will now be enforced due to the Final Rule)
  - $10,000 (increasing – to $11,383) per infraction
  - If not corrected within 30 days, $10,000 (increasing – to $11,383) per day thereafter
- Per the NIH
  - Loss of NIH funding for the investigator
  - Loss of NIH funding for the institution
  - Public listing of non-compliant investigators, clinical trial and institutions on the ClinicalTrials.gov website
- Per Medicare
  - Failure to register – Medicare won't pay/reimburse for appropriate research costs
- For some journals
  - Failure to register – Will not accept manuscript

Clinical Trial Cancer Mission 2020 Act



113TH CONGRESS
1ST SESSION

H. R. 2301

To amend the Public Health Service Act to enhance the clinical trial registry data bank reporting requirements and enforcement measures.

IN THE HOUSE OF REPRESENTATIVES

JUNE 6, 2013

Mr. REED (for himself, Ms. SLAUGHTER, and Mr. COLLINS of New York) introduced the following bill; which was referred to the Committee on Energy and Commerce

A BILL

To amend the Public Health Service Act to enhance the clinical trial registry data bank reporting requirements and enforcement measures.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the "Clinical Trial Cancer Mission 2020 Act".

Intended to strengthen cancer research results reporting requirements

Grantees not reporting trial results within required timeframe lose eligibility for add'l funding of current grant

Will not be eligible for future grants

May be required to repay grant

New features

- Reporting relatedness of AE/SAE events to study product/device/procedure
- Listing of deaths separately
- Options to include ethnicity and race
- Submitting to Clinicaltrials.gov the protocol and the statistical analysis plan at the end of the study. (also, at the end of the study, IRB approvals and approved consent forms may be required)

Challenges

- The principal investigator is held responsible for registering and results reporting.
- Staff can be delegated the task of entering the registration information and results data, but the Principal Investigator is fully responsible for the approval and release of the records.
- The greatest challenge for registration: writing appropriate outcome measures
- The greatest challenge for results reporting: having the summary results ready for entry into ClinicalTrials.gov
- Less ClinicalTrials.gov review – more burden on the PI

Why should you care?

- Penalty enforcement
- Journals request/require
- Medicare requires
- ..it is the law..

Available Support!

To support UAB staff and faculty in complying with FDAAA, the CCTS will provide support in several ways:

- train and guidance for FDAAA implementation
- support and completion of registration of clinical trials records for investigators, if requested
- support and assist investigators with results reporting
- assist and provide guidance to the IRB in identification of Applicable Clinical Trials

Services we can provide

- Obtain password access to enter a new protocol or update one already registered (or regenerate a new one if needed!)
- One on one training with research teams
- Presentations for large groups
- Assistance with entering information
- Assistance with interpreting review comments
- Suggestions on completing data fields.
- Assistance with finding assistance!

Who to contact

- Penny Jester (pjester@uab.edu)
- Karen Allen (Cancer Center Studies) (karenallen@uab.edu)
- Ilet Dale (idale@peds.uab.edu)
- CCTS (ccts@uab.edu)

References

- Zarin D A, Tse T, Williams, R J, Carr S. Trial Reporting in ClinicalTrials.gov – The Final Rule. N Engl J Med, 2016.
- Hudson K L, Lauer M S, Collins F S. Toward a New Era of Trust and Transparency in Clinical Trials. JAMA, Sept 2016.
- ClinicalTrials.gov. Review criteria and other support materials (https://clinicaltrials.gov/ct2/manage-recs/resources#ReviewCriteria).