ClinicalTrials.gov Compliance Issues

BMC/BU Medical Campus – Clinical Research Seminar

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Boston Medical Center is the primary teaching affiliate
of the Boston University School of Medicine.

PRESENTATION OVERVIEW

- Explain the Final HHS Rule and the NIH Policy regarding registration and results submissions to ClinicalTrials.gov
- Highlight the requirements for Responsible Party (PI) when BMC or BU Medical Campus is the Sponsor
- Describe the process to facilitate ClinicalTrials.gov compliance at BMC – BU Medical Campus

CLINICALTRIALS.GOV – ENHANCE AVAILABILITY OF INFORMATION TO THE PUBLIC

- ClinicalTrials.gov is a website maintained by the National Library of Medicine (NLM) at the National Institutes of Health (NIH)
- ClinicalTrials.gov was launched in 2000 in response to FDA Modernization Act of 1997, which required HHS, through NIH, to establish a clinical trials registry
- In 2005, International Committee of Medical Journal Editors (ICMJE) began requiring trial registration as a condition of publication
- In 2008, ClinicalTrials.gov released its results database in response to the FDA Amendments Act of 2007 (FDAAA), which expanded the requirements to include result reporting for trials involving FDA regulated products
- Effective January 1, 2014, CMS required mandatory reporting of NCT on claims for items and services provided in clinical trials that are qualified for coverage under the Medicare Clinical Trial Policy (“Qualifying Clinical Trials”)

CLINICALTRIALS.GOV – ENHANCE AVAILABILITY OF INFORMATION TO THE PUBLIC

- On September 16, 2016, HHS issued the final rule for Clinical Trials Registration and Results Information Submission, which clarified and expanded the registration and results submission requirements in accordance with FDAAA (the “Final Rule”)

  https://www.federalregister.gov/documents/2016/09/21/2016-22129/clinical-trials-registration-and-results-information-submission

- On same date, NIH published a Policy, which requires registration and result reporting of all NIH funded clinical trials (the “NIH Policy”)
  https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-149.html NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information

- The NIH Policy complements the Final Rule

- Both the Final Rule and the NIH Policy go into effect today (January 18, 2017)

THE NEW NIH POLICY - TRANSPARENCY

- Contribute to scientific knowledge
  - Avoid repeating trials that were unsafe or unsuccessful
  - Helps verify findings of others
  - Preserves scientific integrity

- Increases public access
  - Encourage participation by others
  - Protects the subject
  - Increases public trust in research

https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-149.html

WHICH TRIALS REQUIRE RESULTS INFORMATION?

- Applicable Clinical Trials (ACT) under FDAAA (The New Rule)
  - For those studies with a **Primary Completion Date** on or after January 18, 2017, results information required regardless of whether FDA regulated product has been approved, licensed or cleared for marketing
  - **Primary Completion Date** is “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.”
- NIH-funded clinical trials initiated (enroll first subject) after January18, 2017 that are supported from grants submitted after that date

WHAT IS AN ACT? USE THE ACT CHECK LIST

Question	Yes	No
1. Is the study interventional (a clinical trial)? *Study Type* data element is "Interventional"	☐	☐
2. Does the study evaluate at least one drug, biological, or device product regulated by the United States Food and Drug Administration (U.S. FDA)? *Studies a U.S. FDA-regulated Device Product* data element is "Yes" and/or *Studies a U.S. FDA-regulated Drug Product* data element is "Yes."	☐	☐
3. Is the study other than a Phase 1 trial of a drug and/or biological product or is the study other than a device feasibility study? For drug product trials, *Study Phase* data element is NOT "Phase 1" and for device product trials, *Primary Purpose* is NOT "Device Feasibility."	☐	☐
4. Do ANY of the following apply (is the answer "Yes" to at least one of the following sub-questions: 4a, 4b, OR 4c)?	☐	☐
a. Is at least one study facility located in the United States or a U.S. territory? *Facility Location – Country* data element is "United States," "American Samoa," "Guam," "Northern Mariana Islands," "Puerto Rico," "U.S. Virgin Islands," or other U.S. territory.		
b. Is the study conducted under a U.S. FDA Investigational New Drug application (IND) or Investigational Device Exemption (IDE)? *U.S. Food and Drug Administration IND or IDE Number* data element is "Yes."		
c. Does the study involve a drug, biological, or device product that is manufactured in and exported from the U.S. (or a U.S. territory) for study in another country? *Product Manufactured in and Exported from the U.S.* data element is "Yes."		

If "Yes" is answered to all 4 questions, and the study was initiated on or after January 18, 2017, the trial would meet the definition of an ACT.

WHAT IS A CLINICAL TRIAL UNDER THE NIH POLICY?

- "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."

- Includes clinical trials that are not "Applicable Clinical Trials"
  - Phase 1 trials of FDA-regulated drugs and biologicals
  - Small feasibility studies of FDA-regulated device products
  - Study of an intervention that is not regulated by the FDA (i.e. behavioral interventions)

https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-149.html

See "NIH Policy on Dissemination of NIH-Funded Clinical Trial Information" Presentation to the Clinical Trials Registration Taskforce, December 15, 2016 by Sarah Carr and Valery Gordon

NIH CLINICAL TRIAL DECISION TREE

- If yes to all of the following, registration and results reporting required
  - Does the study involve human participants?
  - Are the participants prospectively assigned to an intervention?
  - Is the study designed to evaluate the effect of the intervention on the participants?
  - Is the effect that will be evaluated a health-related, biomedical, or behavioral outcome?
- Does not include observational and natural history studies

See *"NIH Policy on Dissemination of NIH-Funded Clinical Trial Information" Presentation to the Clinical Trials Registration Taskforce, December 15, 2016 by Sarah Carr and Valery Gordon*

WHO IS RESPONSIBLE FOR REGISTERING, UPDATING AND SUBMITTING RESULTS?

- The Responsible Party is the awardee or investigator for NIH-funded clinical trial (subawardees and subinvestigators must coordinate with RP)

- When BMC or BU Medical Campus is the sponsor (no outside funding, NIH grantee) they will designate the PI as RP
  - To be RP, PI must
    - Be responsible for conducting the trial
    - Have access to and control over the trial data
    - Have the right to publish the trial results; and
    - Have the ability to meet the ClinicalTrials.gov requirements for submitting and updating trial information

WHAT ARE THE RP'S OBLIGATIONS UNDER THE NEW RULE AND THE NIH POLICY?

- Register the clinical trial
  - Final Rule + NIH Policy no later than 21 days after enrollment
  - For ICMEJE prior to the enrollment of the first participant
  - For QCT prior to enrollment of the first participant

  REGISTER PRIOR TO ENROLLMENT FOR ALL

- For Final Rule and NIH Policy update on at least once every 12 months (some information within 15 or 30 days of change i.e. recruitment status, Primary Completion Date)

- For Final Rule and NIH Policy, submit summary results, which includes adverse events information, not later than 12 months after the Primary Completion Date (delays allowed under certain circumstances)

REQUIRED CLINICAL TRIAL RESULTS INFORMATION FOR ACTS AND NIH FUNDED CLINICAL TRIALS

(1) Participant Flow
(2) Demographic and baseline characteristics
(3) Outcomes and statistical analyses
(4) Adverse event information
(5) Protocol and statistical analysis plan (new requirement)
(6) Administrative information
(7) Additional information for applicable device clinical trials of unapproved or uncleared devices

Look at the instructions and the templates before the trial starts to make sure the data is collected to facilitate compliance with the results information requirements

NIH POLICY COMPLIANCE

- Policy requires plan for compliance in grant application
- Salaries of administrative and clerical staff who assist PIs in meeting their responsibilities may be included in application budget and budget justification as direct cost
- Requirements for clinical trial registration and results submission will be included in the terms and conditions of the award
- Must certify compliance with registration and results requirements in grant progress report forms
- Failure to comply with terms and conditions of award may provide basis for enforcement actions (45 C.F.R. 75.371 – Remedies for noncompliance for HHS awarding agency or pass-through entity)
  - Temporarily withhold payments pending correction
  - Suspend or terminate award
  - Withhold further awards for the project or program

NIH-FUNDED ACT AND NEW RULE COMPLIANCE

- If NIH-funded clinical trial is also an ACT, non-compliant with 42 USC 282(j) (FDAAA) and 42 CFR Part 11.66 (Final Rule)
  - HHS agency will verify compliance, and if not compliant, any remaining funding for grant or funding for a future grant to such grantee will not be released
  - HHS agency will provide notice to grantee of non-compliance and allow 30 days to correct

- Other ACT
  - Failure to certify compliance and failure to submit required information are violations of Food, Drug and Cosmetic Act
  - Civil monetary penalties of up to $10,000/day
  - Have until April 18, 2017 to be compliant

PROCESS AT BMC – BU MEDICAL CAMPUS

- Administered through the BMC – BU Medical Campus Office of Human Research Affairs (OHRA)
- Process will be documented in a joint policy, which will be circulated when finalized
- Studies to Register
  - NIH-Funded Clinical Trials (results information needed)
  - Trials Meeting ICMJE Definition
  - Qualifying Clinical Trials (QCT) (those that submit claims to CMS)
  - Applicable Clinical Trials (ACT) (results information needed)
- Studies should be registered in ClinicalTrials.gov concurrently with IRB submission
- NCT number should be provided to IRB and BMC CTO for trials using BMC clinical infrastructure

PROCESS AT BMC – BU MEDICAL CAMPUS

- Departing PIs will need a transition plan for ongoing studies in ClinicalTrials.gov
- Registration through the PRS (Protocol Registration and Results System) institutional administrator
  - Karla Damus for each of BMC and BU Medical Campus, if not available
    - Ellen Jamieson or Joyce Samet for BMC
    - Mary-Tara Roth for BU Medical Campus
- BMC non-compliance escalated to BMC Research Compliance officer then to BMC Institutional Official
- BU Medical Campus non-compliance escalated by CRRO, Director to BU Medical Campus Institutional Official
- Training, education, and compliance monitoring will be provided by OHRA

SUPPORTING RESEARCHERS WITH THE PROCESS AT BMC–BU MEDICAL CAMPUS

- Assist PIs in determining if their study is a clinical trial and the type of trial
- Assist in registration and reporting results
- Regular auditing and monitoring for compliance
- Training and education for PIs and research staff provided by OHRA/CRRO
  - Annually, present a CRRO Seminar on ClinicalTrials.gov Integrate key information into CRRO trainings (PI and Fundamentals)
  - Educational venues developed for BMC/BU Medical Campus Research Professional Network (RPN) and the BMC Research Managers
  - Departmental presentations to research faculty on request
  - Website with ClinicalTrials.gov information, links, and resources (e.g. checklists, algorithms, templates, videos, publications)
  - CRRO consultations from the design of clinical trials throughout the registration, updating and results reporting process

REGISTRATION AND RESULTS REPORTING REQUIREMENTS ON CLINICALTRIALS.GOV

Element	Final rule	NIH Policy
Intervention/phase type	Drug, biologic, device products regulated by FDA; not phase 1	All, including behavioral interventions; all phases
Timeframe- registration	Not later than 21 days after enrollment of the first subject	Same
Registration data elements	Consists of descriptive information, recruitment information, location and contact information, and administrative data.	Same
Timeframe- results reporting	Not later than 12 months after primary completion date	Same
Results data elements	Includes participant flow, demographic and baseline characteristics, outcomes and statistical analyses, adverse events, the protocol and statistical analysis plan, and administrative information.	Same
Effective Date	Jan 18, 2017; Compliance by April 18, 2017	Jan 18, 2017

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

ICMJE Policy (effective 2005) –No change. Registration required for all phases of clinical trials of all interventions with any funding source. Enforcement is refusal to publish.

Clinical Trials.gov currently has more than 224,000 study record, 23,000 of which display results information.
The value of prospective trial registration and structured results information reporting is widely recognized.
The ultimate goal of conducting human experiments is to contribute findings to the evidence base that informs future medical care. Unreported trials, or those reported in an imprecise or incomplete manner, generally have limited to no societal value.
The final rule and the NIH policy hold all parties responsible for clinical trials- not just the investigators accountable. Academic medical centers and other organizations will need to ensure that their system, procedures, and organizational values all promote complete and timely clinical trial reporting.

Zarin DA, et al. "Trial Reporting in Clinical Trials.gov– The Final Rule". NEJM 2016,375:20, 1998-2004.

A significant proportion of completed studies within the ClinicalTrilas.gov database did not achieve public disclosure of results (PDOR) within 4 years of follow-up, especially smaller studies at earlier stages of development with industry funding. This constitutes reporting bias and threatens the validity of the clinical research literature in the US.

Saito H and Gill CJ. "How Frequently do the Results from Completed US Clinical Trials enter the Public Domain? A Statistical Analysis of the ClinicalTrials.gov Database". PLOS One July 2014 9(7) e101826.

Roughly half of investigational drugs entering late-stage clinical development fail during or after pivotal clinical trials, primarily because of concerns about safety, efficacy, or both. Results for the majority of studies of investigational drugs that fail are not published in peer-reviewed journals.

Hwang TJ, et al. "Failure of Investigational Drugs in Late-Stage Clinical Development and Publication of Trial Results". JAMA Internal Med, 2016:176(12):1826-33.

Boston University Medical Campus and Boston Medical Center:
Clinical Research Resources Office

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Welcome! We're here to help you in your clinical and human research.

The mission of the Clinical Research Resources Office is to facilitate the design and conduct of ethical and scientifically valid clinical and human research by providing a range of services, resources and guidance to support BMC and BU Medical Campus clinical researchers in planning, submitting, conducting and analyzing their research. In fulfilling this mission, the CRRO strives to:

- **Facilitate research** by providing guidance and tools that are relevant, focused, accessible, and current.
- **Be responsive to needs** of the BMC and BU Medical Campus clinical research community, the needs of research participants, and the changes in regulations and policies guiding human research.
- **Centralize expertise and support** for the conduct of human research.
- **Support & enhance the research workforce** infrastructure to maximize quality of research.
- **Foster research participant advocacy** by promotion of best practices to ensure the safe and ethical conduct of human research.

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www.bumc.bu.edu/crro/

Boston University Medical Campus and Boston Medical Center:
Office of Human Research Affairs

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Trial Registration and Results Reporting on ClinicalTrials.gov

Registration and summary results reporting of clinical trials has two main purposes: to inform potential subjects, and to increase the likelihood that negative results of trials will be publicized. The U.S. Government site for registering clinical trials is ClinicalTrials.gov. A study is issued a CT.gov NCT registration number when it is registered. A trial only needs to be listed once. For investigator-initiated clinical trials, the Principal Investigator is considered the Responsible Party, and is the one who has to complete the registration. For multi-center clinical trials, someone other than the local PI usually fulfills this responsibility. The Responsible Party who initially registered the clinical trial is also the one who must maintain the information about the trial, including updating recruitment information at least every 12 months and reporting final results.

To find out whether the rules and policies apply to your research click here.

Summary of HHS Final Rule and NIH Policy on Registration/Reporting in ClinicalTrials.gov in NEJM (Nov. 2016)

For more information about the registration process, see the ClinicalTrials.gov website.

For assistance:

- About Us
- HRPP Policies
- Clinical Data Warehouse
- Required Training
- Audits
- Funding Opportunities
- ClinicalTrials.gov
  - Trial Registration and Results Reporting on ClinicalTrials.gov
  - Registration and Results Reporting: Who and How
  - Helpful ClinicalTrials.gov guidance
- For Research Participants

www.bumc.bu.edu/ohra/clinicaltrials-gov/

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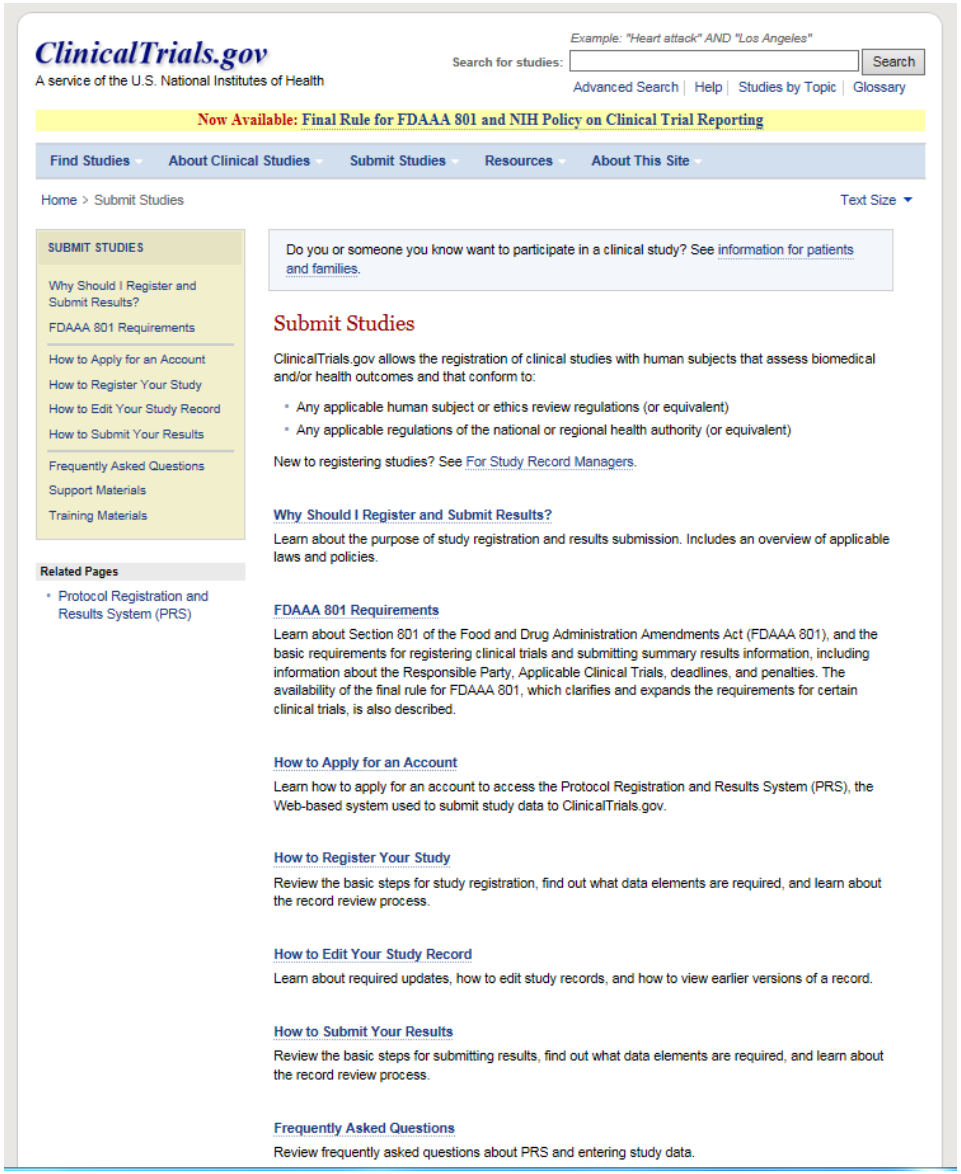

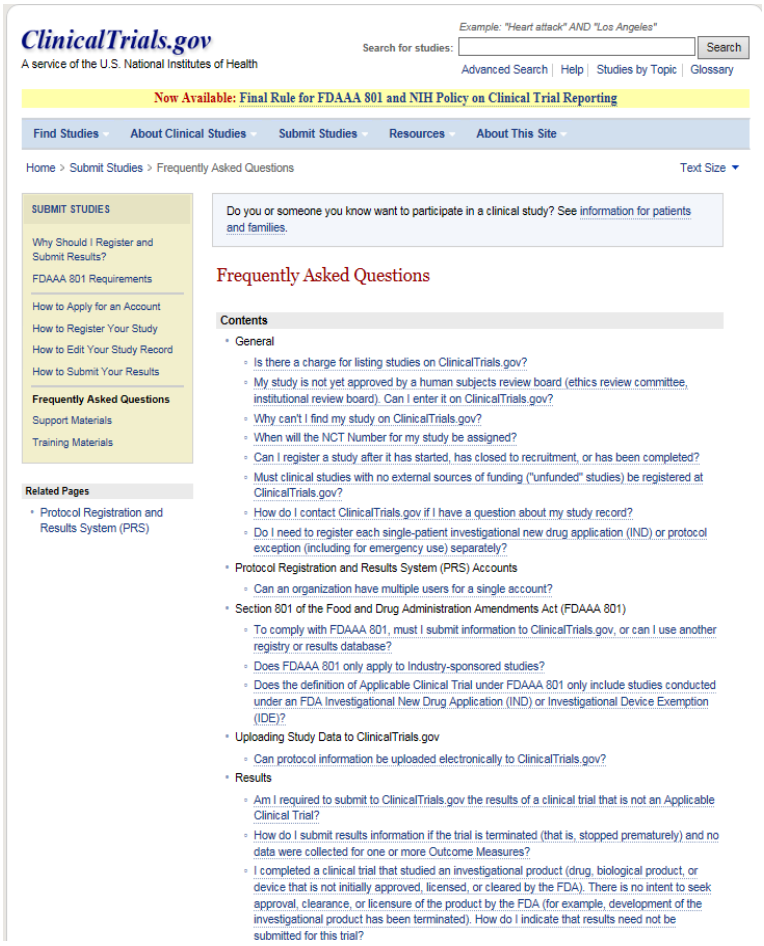

https://clinicaltrials.gov

NEWS RELEASES

Friday, September 16, 2016

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 Administration-regulated drug, biological and device products. At the same time, the National Institutes of Health has issued a complementary policy pdf for registering and submitting summary results information to ClinicalTrials.gov for all NIH-funded trials, including those not subject to the final rule.

"Access to more information about clinical trials is good for patients, the public and science," said NIH Director Francis S. Collins, M.D., Ph.D. "The final rule and NIH policy we have issued today will help maximize the value of clinical trials, whether publicly or privately supported, and help us honor our commitments to trial participants, who do so much to help society advance knowledge and improve health."

Clinical trials are vital to medical advances because they test new and existing health-related interventions, helping us understand whether they are safe and effective in humans when used as intended. Some clinical trials provide information about which medical treatments work best for certain illnesses or certain groups of people.

Expanding the registration information in ClinicalTrials.gov improves people's ability to find clinical trials in which they may be able to participate and access investigational therapies. More information about the scientific results of trials, whether positive or negative, may help inform healthcare providers and patients regarding medical decisions. Additional information will help researchers avoid unnecessary duplication of studies, focus on areas in need of study and improve study designs, ultimately advancing the development of clinical interventions.

Institute/Center

NIH Office of the Director (OD)

Contact

NIH News Media Branch
301-496-5787

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 Clinical Trial Registration and Results Information Submission
- NIH Director's Blog: Clinical Trials – Sharing of Data and Living Up to Our End of the Bargain
- ClinicalTrials.gov

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RESOURCES

- https://clinicaltrials.gov/
- www.bumc.bu.edu/ohra/clinicaltrials-gov/
- www.nih.gov/news-events/news-releases/hhs-take-steps-provide-more-information-about-clinical-trials-public
- www.nih.gov/news-events/news-releases/hhs-take-steps-provide-more-information-about-clinical-trials-public
- Zarin DA, et al. "Trial Reporting in Clinical Trials.gov– The Final Rule". NEJM 2016,375:20, 1998-2004. www.nejm.org/doi/full/10.1056/NEJMsr1611785
- www.nih.gov/news-events/summary-hhs-nih-initiatives-enhance-availability-clinical-trial-information

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