

# ClinicalTrials.gov: The Push for More Transparency

*and*

*How Your Institution Can Keep Up with the Expanded Requirements,  
Tackle Systematic Changes, and Prepare for Enforcement*

HCCA Research Compliance Conference

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## Outline

- Purpose of expanded requirements
- Overview of the most impactful changes
  - NIH Policy
  - HHS Final Rule
- Strategies for Managing an Institution's Account
- Resources



## Extra! Extra!

New Requirements went into effect on January 18, 2017:

- New NIH Policy
- Final Rule ((regulation 42 CFR Part 11) expands requirements under federal law FDAAA)



Final Rule enforceable as of April 18, 2017



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## Reminder: Journal Requirement stays the same

**ICMJE** INTERNATIONAL COMMITTEE of  
MEDICAL JOURNAL EDITORS

- Which studies are required to register?
  - any research study that prospectively assigns human participants to health-related interventions to evaluate the effects on biomedical or health-related outcomes
- Must register before 1<sup>st</sup> subject is enrolled
- Registration required – Result reporting **encouraged** not required
- ICMJE does **not** consider results data posted on ClinicalTrials.gov as prior publication

See Int'l Committee of Medical Journal Editors (ICMJE) <http://www.icmje.org/about-icmje/faqs/clinical-trials-registration/>



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## Paradigm Shift

- Traditionally, investigators decided whether, when and how to report results
  - Many studies never reported
  - Cherry picking of outcome measures and adverse events
- Under FDAAA and NIH policy
  - Registration and results reporting must be done on legally defined timeline
  - Organizations that sponsor studies will be held responsible
    - Requires fundamental changes throughout the CRE: funders, sponsors, investigators
- Greater transparency into human experimentation
  - The time to decide if a study is worth reporting is BEFORE the participants are put at risk, not AFTER

CRE = clinical research enterprise

Source: Slide 8 from ClinicalTrials.gov Webinar, Overview of the Final Rule - Webinar 1 of 3, Sept. 27, 2016.



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## In Striving for Transparency, the New Requirements:

- 1) Expand the scope of trials that need to register and report results
- 2) Expand what information must be submitted in the database
- 3) Clarify timelines for data submission and response to QA comments
- 4) Facilitate enforcement
- 5) Require notification to study participants of ClinicalTrials.gov postings via Informed Consent



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## Expanding the Scope – NIH Policy

- All NIH defined “clinical trials” funded wholly or partially by NIH must register and post results.
  - K awards & T-32 included.
  - If NIH funding is only for infrastructure, policy does not apply.
- NIH “clinical trial” 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.”*

NIH Policy, p. 24. <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-015.html>



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## NIH Policy – Scope is broader than Final Rule

- Type of intervention does not matter
  - E.g. Behavioral Study
    - intervention for weight loss control: Community based random assignment with public awareness campaigns and educational pamphlets about smoking to assess smoking behavior
- Study phase does not matter
  - Exploratory and phase 1 drug studies included/ Device feasibility studies included

NIH Clinical Trial Definition: Case Studies (2015) :  
<http://osp.od.nih.gov/sites/default/files/resources/CaseStudies-2015UPDATED.pdf>



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## Expanding the Scope – Final Rule

- Results reporting for ACTs is required regardless of approval status of the studied products.
- Previously, results reporting was required for products that were approved/cleared (for any use).

Final Rule ACT checklist: [https://prsinfo.clinicaltrials.gov/ACT\\_Checklist.pdf](https://prsinfo.clinicaltrials.gov/ACT_Checklist.pdf)

*Note: Checklist supersedes the ACT section of the Elaboration of Definitions document from 2009 which is posted on ClinicalTrials.gov website for its useful discussion of Responsible Party: <https://prsinfo.clinicaltrials.gov/ElaborationsOnDefinitions.pdf>*



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## Notifying Participants via Informed Consent

- FDA Mandated Consent Form Language for Applicable Clinical Trials (since 2012):
  - “A description of this clinical trial will be available on [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov), as required by US law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.” 21 CFR 50.25(c)
- Now NIH policy also requires that Clinicaltrials.gov **must be referenced in informed consent document**



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## Expanded Information Required for Registration

### Examples:

- New menu options to clarify primary purpose of the study:
  - Primary purpose of the clinical trial is NOT device feasibility
  - Primary purpose is NOT to conduct a phase one drug study

*This will help with ACT determination*
- Other elements
  - Details on study design
  - If study ended prematurely, the reason why



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## Expanded Information Required for Registration (Devices)

Under FDAAA, NIH is prohibited from posting registration information for device ACTs that have not been previously approved or cleared by the FDA, unless the Responsible Party affirmatively elects to have the registration posted.



### Under Final Rule, Additional Data Element for device trials:

- If FDA regulated device product
- If FDA device product not approved or cleared by the FDA
- If ok to post registration prior to FDA approval or clearance



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## Expanded Information Required for Results

- Baseline characteristics
  - Same as before: age and gender information required
  - Under Final Rule, new baseline information required:
    - Race
    - Ethnic background (if collected) and
    - Any other measures assessed at baseline and used in the analysis of the primary outcome measures
- Adverse Event (AE) Information
  - Information on process/method of AE collection
    - Time frame over which AEs were collected
    - Description of AE reporting method and collection approach
  - Table of number and frequency of deaths due to any cause by treatment or comparison drop



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## Expanded Information Required for Results



### New uploading requirement

- A copy of the protocol & statistical analysis plan will be required at same time as results posting.
- RP may redact:
  - Names/addresses/personally identifiable information
  - Trade secrets / confidential commercial information

42 CFR § 11.48(a) (5)

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



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## Clarification of Timelines for 30 day Updates

- Change of study enrollment status
- Study start date
- Intervention name, if it changes
- Availability of expanded access (manufacturers only)
- Individual site status
- Primary Completion Date and Study Completion Date
- IRB status
- Contact information
- Errors
- Amendments that affect anything listed in ClinicalTrials.gov



42 CFR § 11.64



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## Clarification of Timelines – Response to QA Comments

### Changes re: ClinicalTrials.gov QA Review Process

- Currently, ClinicalTrials.gov does not post any submitted information that did not fulfill its quality-control review criteria.
- Under Final Rule:
  - ClinicalTrials.gov will post all submitted information on the public database no later than 30 days after receipt **even if there are outstanding quality issues.**
  - Responsible Parties will have 15 days to correct registration records and 25 days to correct results information based on Major comments. (***Advisory comments*** are suggestions for improvements but do not have to be addressed.)
  - Information will be posted publically with a **disclaimer** that information posted does not meet the quality control review criteria

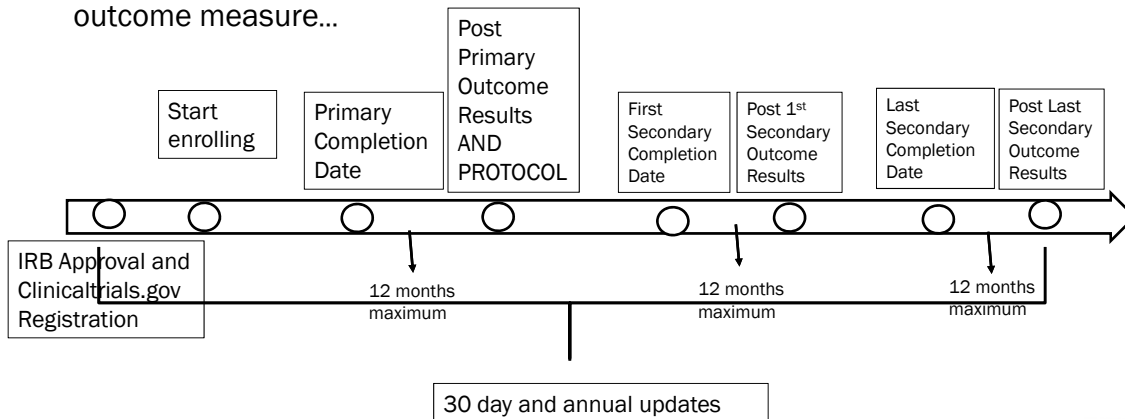


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## Clarification of Timelines for Results Reporting

Results due: 12 months after final subject examined or receives intervention for the purpose of final collection of data for that secondary outcome measure...



## Are your protocols ready for public consumption?

- Clearly Defined Outcome Measures (not Aims and Objectives)
- Specification of Primary, Secondary vs. Other or Exploratory measures. See 42 CFR §11.10(a).  
Spirit Checklist or NIH Protocol Templates can help.
- Organized and clear. Without ambiguities. Proofread.



OR



## Compliance Enforcement – Final Rule

42 CFR 11.66\*:



- Identifying non-compliant records on ClinicalTrials.gov
- Monetary fines: \$11,383/day/infraction
- Potential criminal sanctions for “failure to comply with requirements of this part...is a prohibited act under 21 USC 331 (ii)

\*HHS has always had the authority to levy monetary fines under FDAAA, this is unchanged.



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## Compliance Enforcement – NIH Policy

- NIH requires dissemination plans (compliance with ClinicalTrials.gov registration and/or reporting requirements) in all new applications and proposals submitted after 1/18/17.
- NIH requires certification of the *grantee institution's ClinicalTrials.gov compliance* in new applications/proposals and annual Progress Reports of existing awards subject to the new policy.
- NIH will not release funding for any new clinical research awards or continuing awards if the grantee institution is not compliant with its ClinicalTrials.gov obligation. NIH will notify institutions of non-compliance.



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# Strategies to Manage Your Institution's ClinicalTrials.gov Account



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## How does your institution determine & designate the Responsible Party (RP)?

- Institution as the RP
- Designate Principal Investigator as RP
  - By policy?
  - By letter?
  - Merely by practice?
- What do you do when an investigator leaves the institution?
- Do you have an offboarding procedure?



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## How does your institution identify records which need to be registered?

- Which office?
  - IRB
  - Research Billing
  - Grants and Contracts
  - Regulatory Office
- When?
  - Before submittal to the IRB? After?
- What are they identifying?
  - Final Rule
  - NIH Policy
  - Others: CMS, ICMJE....
- How?
  - IRB application language
  - Other means?

**Note:** Under 21 CFR §50.25 (c), IRBs must consider which trials fall under 42 CFR 11 and must use specified language regarding ClinicalTrials.gov language in their informed consents.



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## Institutional methods to prevent problem records

- Notifying investigators of upcoming obligations
  - as shown by the Planning Report
  - related to business process of trials
- Training and Education
- Bio-statistical Support
- ClinicalTrials.gov designated FTE
  - Quality Assurance of registrations
  - Help investigator troubleshoot database or add PRS comments
  - Data entry
- Creation of additional tools



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## Using a Clinical Trial Management System (CTMS)

- Does your institution have one?
- Can it trigger flags for:
  - Study status changes
  - Site status changes
  - Personnel changes
  - Relevant amendments

**Tip:** Watch for Definitions that “almost match” between CTMS and ClinicalTrials.gov (e.g. completion date vs. primary completion date)



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## Using the Planning Report to prevent problems

### Outreach to Responsible Party and team

- Primary Completion Date – anticipated Results due for ACTs and pACTs
- Update expected fields to prevent Not Recently Updated
- Corrections Expected Date for Major Comments which must be addressed

### Limitations:

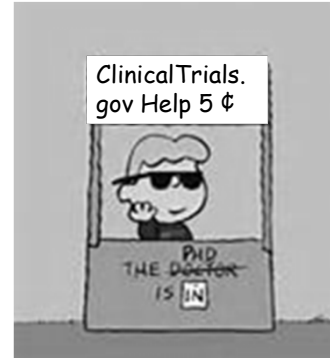
- It may not be able to flag the right NIH funded trials:
  - Multiple complexities: Types of awards (including training grants) and award date
- It will not be able to know when you need a study-specific update



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## Training and Tools...

- Conceptual Workshops/Outreach to PIs or Departments
- Training workshops
  - Templates available for basic concepts
  - Step by step workshops with Example Studies from the [Training Materials](#) and [PRS Test system](#)
  - Build a record workshops
- Office hours
- FAQs
- Templates or checklists for guidance
- Statistical support or back up



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**For those records on the institution's "problem list"....**

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## Tackling non-Compliance

- Prioritizing which problems to tackle first
- Outreach to Responsible Parties
- Escalating Non-Compliance
- Consequence to RP if unable to fulfill RP responsibilities



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## Using the Problem Report to Address Non- Compliance

- Data Entry Issues
  - PRS Review Comments Time-sensitive attention needed, becomes regulatory.
  - Entry Not Completed Data completion issue
  - Not Recently Updated Regulatory problem, per se.
  - Record Has Errors Regulatory problem, per se.
- FDAAA 801 Issues
  - Missing FDAAA Information
  - Late Results - per FDAAA } Regulatory problem, per se, if it really is an ACT
- Administrator Issues
  - Ready for Review and Approval
  - Never Released
  - Update Not Released } Data Completion or processing issues



The Problem Report does not yet address NIH funded trials that need results reporting unless they happen to be ACTs.



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## Challenges: Opportunities from Institutional Perspective

- Data collected in many different ways
  - Benefits of having services that build more standardized and efficient templates available
- AE Reporting – often still done manually despite XL Upload feature
- Not all studies have a biostatistician
- Clinical Trials Management Systems have potential for long term efficiency. However many challenges to getting there:
  - Choose one that works w/ systems already in place at organization
  - Different definitions of similar terms
  - Cost of systems



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## Challenges: Opportunities from Institutional Perspective

- Investigators prioritizing registration and results reporting
- The ClinicalTrials.gov database is challenging to use
  - Just complicated enough that there is a learning curve; especially if investigator only reports results 1 – 2 times a year or less;
  - Investigator knows the study best; it may be hard to hand it off to someone with less study-specific knowledge
- Finding the sweet spot: Who should do which parts of the work across the institution?



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## Challenges from investigator perspective

- Hard to accurately portray what is happening in a trial in the ClinicalTrials.gov system
- No options for graphs/ qualitative results, especially for mixed methods research
- Terminated studies still need results reporting



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## Possible additional changes coming...

- Protocol Upload guidance (coming soon...)
- Addition of NIH funded Trials to the Planning Report (hopefully!)
- XML uploads of adverse events from Redcap or other data capture systems
- Informed Consent uploads (due to New Common Rule)
- Future pushes for more data transparency: individual level data sharing plans:



Clinical trials that begin enrolling participants on or after 1 January 2019 must include a data sharing plan in the trial's registration.

[http://www.icmje.org/news-and-editorials/data\\_sharing\\_june\\_2017.pdf](http://www.icmje.org/news-and-editorials/data_sharing_june_2017.pdf)



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## Clinical Trials Registration Taskforce

- *Membership:* Clinical trial registration experts at Academic Medical Centers (AMC)
  - Taskforce of the former CTSA consortium
  - Over 200 members. Monthly call with ~ 75 participants each call.
  - ‘On our own’ since Feb 2014
    - Support from the Harvard Clinical and Translational Science Center (Harvard Catalyst) and dedicated Taskforce members
- *Focus:* Clinical trials registration and results reporting that affect US AMCs
- *Objectives:*
  - Identify best practices
  - Develop tools for regulatory support and investigators
  - Serve as a communication forum



Email Sarah White ([swhite12@partners.org](mailto:swhite12@partners.org)) to join.



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## Questions?

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## Resources

- Summary of Requirements on Research Navigator
- HHS News Release: Final Rule and NIH Policy: <https://www.nih.gov/news-events/news-releases/hhs-take-steps-provide-more-information-about-clinical-trials-public>
- ClinicalTrials.gov Final Rule Webinars 1-3: <https://clinicaltrials.gov/ct2/manage-recs/present#FinalRuleWebinar>
- National Institutes of Health (NIH): Checklist and Elaboration for Evaluating Whether a Clinical Trial or Study is an Applicable Clinical Trial (PDF) (December 2016)

