Registering Clinical Trials: The what, when, where and why

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Oswald Tetteh, Clinical Research Compliance Specialist
What needs to be registered?

• Any research study meeting the definition of a clinical trial
  — International Committee for Medical Journal Editors (ICMJE)
  — Food and Drug Administration Amendments Act (FDAAA)
  — National Institutes of Health (NIH)

• Any research study with funding from an agency that requires registration

• Sub categorization of studies
  — applicable and non applicable clinical trials
  — phase of clinical trial
“The ICMJE defines a clinical trial as any research project that prospectively assigns people or a group of people to an intervention, with or without concurrent comparison or control groups, to study the relationship between a health-related intervention and a health outcome.”

- **Health-related interventions** - drugs, surgical procedures, devices, behavioral treatments, educational programs, dietary interventions, quality improvement interventions, and process-of-care changes

- **Health outcomes** are any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events.
## “Applicable Clinical Trials” per FDAAA

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Is the study intervention (a clinical trial)?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Study Type</em> data element is “Interventional”</td>
<td></td>
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</tr>
<tr>
<td><strong>2. Do ANY of the following apply (is the answer “Yes” to at least one of the following sub-questions: 2a, 2b, or 2c)?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Is at least one study facility located in the United States or a U.S. territory?</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Facility Location – Country</em> data element is “United States,” “American Samoa,” “Guam,” “Northern Mariana Islands,” “Puerto Rico,” “U.S. Virgin Islands,” or other U.S. territory.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Is the study conducted under a U.S. FDA Investigational New Drug application (IND) or Investigational Device Exemption (IDE)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>U.S. Food and Drug Administration IND or IDE Number</em> data element is “Yes.”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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?</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Product Manufactured in and Exported from the U.S.</em> data element is “Yes.”</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>3. Does the study evaluate at least one drug, biological, or device product regulated by the United States Food and Drug Administration (U.S. FDA)?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Studies a U.S. FDA-regulated Device Product</em> data element is “Yes” and/or <em>Studies a U.S. FDA-regulated Drug Product</em> data element is “Yes.”</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>4. 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?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For drug product trials, <em>Study Phase</em> data element is NOT “Phase 1” and for device product trials, <em>Primary Purpose</em> is NOT “Device Feasibility.”</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Identifying an ACT under FDAAA

[https://prsinfo.clinicaltrials.gov/ACT_Checklist.pdf](https://prsinfo.clinicaltrials.gov/ACT_Checklist.pdf)
NIH Definition of a Clinical Trial

• 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.

https://grants.nih.gov/policy/clinical-trials/definition.htm
Trials that meet the NIH Definition of a Clinical Trial

If you answer “yes” to the following questions, your study meets the NIH definition of a clinical trial and registration and results reporting ARE REQUIRED.

1. Does the study involve human participants?
2. Are the participants prospectively assigned to an intervention?
3. Is the study designed to evaluate the effect of the intervention on the participants?
4. Is the effect being evaluated a health-related biomedical or behavioral outcome?

If you answered YES to all 4 the NIH Criteria (on the left), your study is a clinical trial even if it is one of the following scenarios:

- Studying healthy participants
- Does not have a comparison group
- Only designed to assess the pharmacokinetics, safety, and/or maximum tolerated dose of an investigational drug
- Behavioral intervention

https://grants.nih.gov/policy/clinical-trials/definition.htm
When do you register?
# Summary of Requirements

<table>
<thead>
<tr>
<th>Entity</th>
<th>Registration</th>
<th>Results Reporting</th>
<th>Penalties</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Health and Human Services (HHS)</strong></td>
<td>Within 21 days of enrollment</td>
<td>Within 365 days of primary completion date for ACTs</td>
<td>• $13,237/study/day&lt;br&gt;• Criminal proceedings&lt;br&gt;• Loss of grant funding</td>
</tr>
<tr>
<td><strong>National Institutes of Health (NIH)</strong></td>
<td>Within 21 days of enrollment</td>
<td>Within 365 days of primary completion date for clinical trials receiving NIH funding</td>
<td>Loss of grant funding (to include the institution)</td>
</tr>
<tr>
<td><strong>National Cancer Institute (NCI)</strong></td>
<td>Within 21 days of enrollment</td>
<td>Within 365 days of primary completion date of NCI-supported clinical trials (in a peer-reviewed journal and/or ClinicalTrials.gov)</td>
<td>Loss of grant funding</td>
</tr>
<tr>
<td><strong>Veterans Health Administration (VHA)</strong></td>
<td>Prior to release of funding. Prior to enrollment</td>
<td>Within 365 days of primary completion date</td>
<td>Loss of grant funding</td>
</tr>
</tbody>
</table>

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**Note:**
- ACTs: Acronyms for the Centers for Medicare and Medicaid Services (CMS) Administration for Clinical Trials (ACTs).
- NIH: National Institutes of Health.
- VHA: Veterans Health Administration.
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<th>Entity</th>
<th>Registration</th>
<th>Results Reporting</th>
<th>Penalties</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Centers for Medicare &amp; Medicaid Services</strong></td>
<td>All qualifying clinical trials</td>
<td>Study-specific</td>
<td>• Coverage denial</td>
</tr>
<tr>
<td>(CMS)</td>
<td></td>
<td></td>
<td>• Costs and fraud investigations</td>
</tr>
<tr>
<td><strong>Patient-Centered Outcomes</strong></td>
<td>All Clinical studies (including observational)</td>
<td>Expected of all PCORI Clinical studies – 500 word abstract published on PCORI website</td>
<td>• Loss of grant funding</td>
</tr>
<tr>
<td><strong>Research Institute</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(PCORI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>International Committee of Medical Journal Editors</strong></td>
<td>Prior to enrollment</td>
<td></td>
<td>Ineligibility to publish</td>
</tr>
<tr>
<td>(ICMJE)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Department of Defense</strong></td>
<td>Prior to enrollment. Prior to release of funding.</td>
<td>Study-specific</td>
<td>• Withholding or recovery of award funds</td>
</tr>
<tr>
<td>(DoD)</td>
<td></td>
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</tbody>
</table>
When do you do updates?
Registering and Updating the Record

- Register the record within **21 days of enrollment** (HHS) –OR- **prior to enrollment** (ICMJE)
- Update the following data elements no later than **30 calendar days after a change occurs**
  - Study start date
  - Intervention name(s)
  - Availability of Expanded Access
  - Expanded Access status
  - Overall recruitment status
  - Explanation for change in status
  - Actual enrollment data
  - Individual site status
  - IRB status
  - Completion Date
  - Responsible Party
  - Official Title
  - Contact Information
Annual Verification

- **Verify** the record **annually** – Record Verification date

JHU enforcement - IRB Continuing Review will be held for studies that are not verified annually
Responding to Comments

- Respond to PRS Review Comments
  within **15 calendar days** (registration) –OR-
  **25 calendar days** (results)
Entering results

- **Report** results within **12 months** of the completion dates.

  - Estimated time to enter results: **up to 40 hours***
  - It may take multiple review cycles to post your results
  - Comments must be responded to within **25 calendar days**

*Primary Completion Date*: the date that the last data point for the primary outcome measure was **collected** from the last enrolled participant.

*Study Completion Date*: the date that the last data point for all remaining outcome measures was **collected** from the last enrolled participant.

*HHS estimated burden statement
According to the revised Common Rule, effective January 21, 2019...

• **Important considerations regarding the uploading of the informed consent form (ICF):**

  • Applies only to clinical trials conducted or supported by a Federal department or agency* using the Common Rule

  • The consent form must have been used in enrolling participants

  • Should be uploaded when recruitment ends and **no later than 60 days** after the last study visit by any subject, as required by the protocol

  • Must be uploaded to either ClinicalTrials.gov or a docket folder on Regulations.gov

Where do you register and do updates?
ClinicalTrials.gov is a database of privately and publicly funded clinical studies conducted around the world.

Explore 273,543 research studies in all 50 states and in 204 countries. ClinicalTrials.gov is a resource provided by the U.S. National Library of Medicine.

IMPORTANT: Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

Before participating in a study, talk to your health care provider and learn about the risks and potential benefits.

- 145,000 unique visitors/day
- 215 million page views/month

Protocol Registration & Results System (PRS)
https://register.clinicaltrials.gov
National Library of Medicine (NLM) is looking for feedback
National Library of Medicine (NLM) is looking for feedback
Why is this necessary?

- Commitment to research participants (including recruitment)
- Scientific validity/transparency
- Ethical standards
- Responsible stewardship of federal funds
- Help IRB assess value of new studies
- Required for journal publication (ICMJE)
- Required by law (FDAAA) and regulations (42 CFR Part 11)
- Required for all NIH-supported clinical trials (including NCI)
- Required for CMS
- Required by WHO
- Required by Foundations, such as Wellcome Trust
Penalties

**Penalties outlined in the FDA Final Rule**

Final Rule (42 CFR Part 11) *Released: 09/2016, Effective: 01/2017, Compliance date: 04/2017*

1. Civil or criminal judicial actions
2. Civil monetary penalties up to $10,000 $12,316 $12,462 $13,237 per study, per day
3. Withholding of current or future funding to organizations that are out of compliance

*These penalties are for any data element FDA determines was, “not submitted as required, or was false or misleading” not just late results*

Publication Recommendations

Trials that meet the clinical trial definition of The International Committee of Medical Journal Editors (ICMJE) that the investigator may wish to publish...

ICMJE journals will consider [for publication] trials beginning on or after July 1, 2005 only if registration occurred before the first patient was enrolled (“prospective registration”)

Many journals follow the ICMJE criteria for publication.

There have been cases within our institution where a manuscript was rejected for publication simply because the study was not registered on ClinicalTrials.gov before enrolling participants!

http://www.icmje.org/about-icmje/faqsc clinical-trials-registration/
FDA Enforcement
FDAAA 801 Violations

- Notice is sent to the Responsible Party
- **Pre-Notice Letters** are **not** identified as an FDAAA 801 Violation and **not** identified in ClinicalTrials.gov
- **Notice of Noncompliance** Letters are identified as an FDAAA 801 Violation in ClinicalTrials.gov

<table>
<thead>
<tr>
<th>Responsible Party/Submitter</th>
<th>NCT Number</th>
<th>Notice of Noncompliance</th>
<th>Response Letter (if any)</th>
<th>Civil Money Penalty Amount (if any)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocugen</td>
<td>NCT03785340</td>
<td>4/15/2022</td>
<td>08/01/2022</td>
<td></td>
</tr>
<tr>
<td>Petrikovets, Andrey M.D.</td>
<td>NCT03052816</td>
<td>8/31/2021</td>
<td>12/20/2021</td>
<td></td>
</tr>
<tr>
<td>Acculis Inc.</td>
<td>NCT03064438</td>
<td>7/26/2021</td>
<td>05/26/2022</td>
<td></td>
</tr>
<tr>
<td>Aceleron Pharma, Inc.</td>
<td>NCT01727336</td>
<td>4/27/2021</td>
<td>12/13/2021</td>
<td></td>
</tr>
</tbody>
</table>

https://www.fda.gov/science-research/fdas-role-clinicaltrialsgov-information/clinicaltrialsgov-notices-noncompliance-and-civil-money-penalty-actions#:~:text=FDA%20has%20the%20authority%20to%20or%20misleading%20clinical%20trial%20information
### Information on FDAAA 801 Violations

<table>
<thead>
<tr>
<th>Available on ClinicalTrials.gov</th>
<th>Issued by FDA</th>
<th>Study Record Submitted</th>
<th>Notice Type</th>
<th>FDAAA 801 Notice</th>
</tr>
</thead>
<tbody>
<tr>
<td>January 6, 2022</td>
<td>December 20, 2021</td>
<td>October 3, 2021</td>
<td>Correction Confirmed by FDA</td>
<td>The responsible party has corrected the violation.</td>
</tr>
<tr>
<td>September 3, 2021</td>
<td>August 31, 2021</td>
<td>December 15, 2018</td>
<td>Violation Identified by FDA</td>
<td>Failure to Submit. The entry for this clinical trial was not complete at the time of submission, as required by law. This may or may not have any bearing on the accuracy of the information in the entry.</td>
</tr>
</tbody>
</table>

More Information: [Notices of Noncompliance (FDA)](https://www.fda.gov/media/151965/download)
Researchers from Yale, Columbia, and Universities Allied for Essential Medicines (UAEM) submitted a Freedom of Information Request
- 58 Preliminary Notice of Noncompliance Letters sent
- 57 for Results, 1 for Registration
- 32 to drug makers
- 0 to Federal Agencies
- 90% reported to ClinicalTrials.gov (median = 3 weeks)
- UAEM released the full text of all 58 letters
Who’s watching?
Watchful Eyes – Stat Report 01/09/2018

Johns Hopkins University

163 of 193 (84%) trials reported late or not at all
49 (30%) results missing in 2015 and 2017
47 (29%) results missing in 2015; posted late as of 2017
8 (5%) results not required in 2015; missing in 2017
14 (9%) results not required in 2015; posted late as of 2017
46 (28%) results posted late before 2015

Percentage of each responsible party's clinical trials that had results reported late or not at all.

TranspariMED/UAEM

Compliance reporting results

- 40 institutions included in analysis
- 2019: 16 = >80%
- 2021: 36 = >80%
  - 2019 = Light blue
  - 2021 = Dark Blue

UAEM: Universities Allied for Essential Medicines
chrome-extension://efaidnmbnmpgatnkkpgfiolcgmleobdn/download/All 2019 2019: Light blue 2021: Dark blue
Clinical Trials Transparency Report_UAEM_v5.pdf
Congress demands that FDA and NIH sanction sponsors that fail to report clinical trial results.

FDA is petitioned to boost enforcement of trial sponsors that fail to register studies or report results.

NIH waste far over $100 million in medical research funding every year – new study.

https://www.transparimed.org/single-post/fdaa-pallone
https://www.transparimed.org/single-post/nih-research-waste
Watchful Eyes – FDAAA TrialsTracker

FDAAA 2007 is a law that requires certain clinical trials to report results. After a long wait, it effectively came into force for all trials due after January 2018. The FDA are not publicly tracking compliance. So we are, here.

Who’s sharing their clinical trial results?

12527 out of 16314

76.8%

US Govt could have imposed fines of at least

$43,442,115,605

Fines claimed by US Govt

$0

https://fdaaa.trialstracker.net/
Tips and Tricks for Entering Data
### Using the Checklist - Registration

#### CLINICALTRIALS.GOV JHU RECORD REVIEW

<table>
<thead>
<tr>
<th>PROTOCOL ID</th>
<th>RECORD OWNER</th>
<th>REVIEWER</th>
<th>Registration</th>
<th>Update status</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT#</td>
<td>Date Released</td>
<td>Comments Date</td>
<td>Reply Date</td>
<td>Date Published</td>
<td></td>
</tr>
</tbody>
</table>

#### GENERAL REVIEW ITEMS

- Record Owner is the PI or Coordinator (SKCCC)
- Contact info for Record Owner is up-to-date
- PI on record matches IRB PI
- NCT# included in IRB "Clinical Trial Information" section
- All Warnings/Errors addressed
- All parenthetical citations have been removed
- All acronyms have been expanded on their first use
- Spell-check complete
- Free-text fields are blank if there is no information to report, and do not contain text such as " TBD," " Pending," " N/A," " None"

#### PROTOCOL SECTION

**STUDY IDENTIFICATION**
- Unique protocol ID is the IRB# or JHU# (JHU Policy)
- Brief Title does not include study type (e.g., Phase I, Randomized...)
- Secondary IDs include NIH grant #s (verify in IRB), and IRB# (SKCCC)

**STUDY STATUS**
- Record Verification Date is the current month/year
- Overall Status matches IRB/CRMS
- Study start data verified with CRMS enrollment data
- Completion Dates Actual/Anticipated have been evaluated for accuracy
- If timeframes for outcomes are the same the primary and study completion dates are identical

#### SPONSOR/COLLABORATORS

- Responsible Party: Sponsor (JHU Policy)
- All sources of support identified in IRB "Support Information" section included as Collaborators
- Full name used and if not recognized, "Unknown" is selected

#### OVERSIGHT

- IND/IDE information completed (if applicable)

#### Verify Human Subjects Review

- Board status verified
- Approval number is a valid IRB number
- Board Name: Office of Human Subjects Institutional Review Boards
- Board Affiliation: Johns Hopkins School of Medicine
- Phone: (410) 955-3000, Email: Pmdsfo@hso.jhu.edu
- Address: 1620 McHenry Street, Reed Hall Suite 8130, Baltimore, MD, 21205

### STUDY DESIGN

- Brief Summary does not unnecessarily duplicate information provided for other data elements
- Brief Summary clearly states the study's hypothesis or the purpose (for Interventional and observational)
- Brief summary and Detailed Description are written in complete sentences with no formatting errors
- Record does not use personal pronouns: "I, we, our, us, they, them, their" becomes "the investigator(s);
- You, your" becomes "the participant(s)

#### CONDITIONS

- Conditions/Focus of study are discrete and does not use verbs or complete sentences
- Keywords are not numbered or bulleted, each condition and keyword is listed individually, one per line

#### ARMS/INTERVENTIONS

- Arm Title or Group/Cohort Label is brief and informative (even if there is only 1 arm)
- Interventions and intervention descriptions are entered correctly
- Arms/Interventions are cross-referenced appropriately

#### OUTCOME MEASURES

- Title is specific and states WHAT is being measured, only 1 variable must be assessed per outcome measure
- Description explains WHAT is being measured, not WHY it is being measured
- Scoring scale name, score range, significance of upper and lower limits specified (if applicable)
- Unit of measure specified
- Time frame specified as a single time point or change between 2 time points
- INCOMPLETE: "Safety and Toxicity", Description: "Safetv of study drug"
  - CORRECT: "Safety as assessed by number of participants experiencing adverse events" Description: "Number of participants experiencing adverse events grade 3 or higher, as defined by Common Terminology Criteria for Adverse Events version 5.0 (CTC v5.0)"

#### ELIGIBILITY

- Age Limits are consistent with the Eligibility criteria and with other parts of the record
- Eligibility criteria is divided into inclusion/exclusion criteria in bulleted format

#### CONTACTS/LOCATIONS

- Central Contact Person specified and accurate (JHU Policy)
- Study Officers match IRB
- All study sites specified matches CRMS
- Recruiting status for each study site accurate (if at least one study site is recruiting the Study Status reflects "Recruiting")
- Each Faculty is listed in a separate field

#### IPD Sharing Statement

- The Plan to Share IPD selection is consistent with the IPD Sharing Plan Description

#### REFERENCES

- Each citation is listed in a separate field (if applicable)
Using the Checklist – Results Entry

Questions?

Please visit our website for tutorials and more detailed information: https://ictr.johnshopkins.edu/clinicaltrials-gov

See us on YouTube at “JohnsHopkinsCTgov”

Email us with any questions at registerclinicaltrials@jhmi.edu