

<b>THE ICAHN SCHOOL OF MEDICINE AT MOUNT SINAI, NEW YORK</b>  <b>STANDARD: POLICY AND GUIDELINES</b>	<b>SUBJECT NO.</b>  <b>ORS-001</b>
<b>DEPARTMENT: Office of Research Services (ORS), ConduITs, Institutes for Translational Sciences</b>  <b>SUBJECT: ClinicalTrials.gov registration and reporting policy</b>	
<b>CROSS-REFERENCE: N/A</b>	

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**Purpose:** To clarify compliance with the federal requirements under the Department of Health and Human Services (DHHS) and NIH regulations and policies on ClinicalTrials.gov registration and reporting for all Mount Sinai Health System staff and medical school faculty, students, and staff conducting or involved in clinical trials research.

**Introduction**

[ClinicalTrials.gov](#) is a public registry aimed at increasing transparency and improving public awareness of research. Information about individual clinical trials is added to ClinicalTrials.gov by registering the trial and reporting results of the trial. It is essential to understand which studies must be registered and who is responsible for ensuring that registration and reporting of results occurs. The following provides detailed information to help you determine if your research should be registered with ClinicalTrials.gov, and if so, offers guidance to meet the requirements for registration and submission of trial results.

Noncompliance with the registration and reporting requirements has serious repercussions for individuals, institutions, and research teams including but not limited to the rejection of manuscript submissions to journals, withholding of grant funds, and/or civil monetary penalties of over \$11,000 per study, per day (subject to inflation).

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**[A. Why is Registration and Submitting Results Required?](#)**

1. **Federal regulations and journal publication** standards require that investigators register certain clinical studies in a publicly accessible database. ClinicalTrials.gov is a publically accessible database to support compliance with such regulations and standards. ClinicalTrials.gov is maintained by the National Library of Medicine at the National Institutes of Health (“NIH”). The agencies that enforce requirements are:
  - a. The Food and Drug Administration (FDA)
  - b. National Institutes of Health (NIH)
  - c. The Centers for Medicare & Medicaid Services (CMS)
  - d. The International Committee of Medical Journal Editors (ICMJE)
- a. The **FDA Amendments Act of 2007** (“FDAAA 801”) In September 2016, the U.S. Department of Health and Human Services issued a **final rule** that clarifies and expands the regulatory requirements and procedures for submitting registration and summary results information of clinical trials on ClinicalTrials.gov, in accordance with **FDAAA 801**. The final rule is intended to make it clear to sponsors, investigators, and the public which trials must be submitted, when they must be submitted, and whether compliance has been achieved. For example, the final rule clarifies the definition of an applicable clinical trial and provides structured criteria for determining which studies meet the definition. The final rule also expands the FDAAA 801 requirements by requiring the submission of results information for trials of unapproved products. The regulation is effective on January 18, 2017 and responsible parties are expected to be in compliance as of April 18, 2017.

- b. The [NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information](#)<sup>12</sup> (“NIH Policy”) 42 CFR part 11 further expands the types of clinical trials that must be registered and have results reported. The NIH Policy requires registration and results submission of all clinical trials funded in whole or part by NIH for applications submitted on or after January 18, 2017.<sup>1</sup>
  - c. The Centers for Medicare & Medicaid Services (CMS) [MLN Matters # SE1344](#) requires the National Clinical Trial Number (NCT#) on claims for items and services provided in “qualified clinical trials” for Medicare coverage.<sup>11</sup>
  - d. The International Committee of Medical Journal Editors (“[ICMJE](#)”) policy (adopted by over 1,000 journals) is broader in scope than FDAAA in requiring which types of trials must be registered. The ICMJE policy applies to research that prospectively assigns human subjects to intervention or comparison groups in order to look at the cause-and-effect relationship between an intervention and a health outcome.
2. ClinicalTrials.gov contains information on publicly and privately funded clinical studies on a wide range of diseases and conditions. The registry aims to support improved transparency and to reduce duplication of effort by a) improving public access to information about clinical trials; b) providing information for clinicians, to help their patients find appropriate trials; and c) providing researchers with an overview of a specific field of research, changes in study design, etc.
  3. It is essential to understand which trials must be registered and who is responsible for ensuring that registration (and reporting of results, if required) takes place.
  4. **Noncompliance** has serious repercussions for individuals, institutions, and research teams including but not limited to:
    - a. FDAAA:
      - i. Public notices of noncompliance and violations
      - ii. Withholding of grant funds
      - iii. FDA sanctions
      - iv. Civil monetary penalties (over \$11,000/study per day – subject to inflation)
    - b. NIH Policy:
      - i. Withholding of NIH funds

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<sup>1</sup> For detailed information, see [Summary of HHS/NIH Initiatives to Enhance Availability of Clinical Trial Information](#), [NIH Clinical Research Policy](#), [NIH Definition of Clinical Trial](#), and [NIH Policy](#) p. 22.

- ii. Termination of grant(s)
- c. ICMJE:
  - i. Cannot publish in journals following ICMJE policy and other select journals
  - ii. Rejection of manuscript
- 5. The resources below provide detailed information to help determine if your trial falls within FDAAA and/or ICMJE requirements for registration and results reporting.

**B. Which Trials Require Registration and Submission of Results to ClinicalTrials.gov?**

**FEDERAL**

Entity	Registration	Results Reporting	Penalties
Food and Drug Administration (FDA)	Within 21 days of enrollment	Within 365 days of primary completion date for ACTs	<ul style="list-style-type: none"> <li>• \$11,569/study/day</li> <li>• Criminal proceedings</li> </ul>
National Institutes of Health (NIH)	Within 21 days of enrollment	Within 365 days of primary completion date for clinical trials receiving NIH funding	Loss of grant funding (to include the institution)
National Cancer Institute (NCI)		Within 365 days of primary completion date of NCI-supported clinical trials (in a peer-reviewed journal and/or ClinicalTrials.gov)	Loss of grant funding
Centers for Medicare & Medicaid Services (CMS)	All qualifying clinical trials		<ul style="list-style-type: none"> <li>• Coverage denial</li> <li>• Costs and fraud investigations</li> </ul>

**OTHER STIPULATIONS**

Entity	Registration	Results Reporting	Penalties
World Health Organization (WHO)	Prior to enrollment	Within 365 days of primary completion date	
International Committee of Medical Journal Editors (ICMJE)	Prior to enrollment		Ineligibility to publish
Foundations (i.e., Gates)	Study-specific		Loss of funds

1. **FDAAA:**

- a. Registration and Results Submission Requirements: FDAAA 801 requires trial registration and results submission for “Applicable Clinical Trials”, which include:<sup>2</sup>
- i. Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations, of a product subject to FDA regulation;
  - ii. Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric post-market surveillance studies; and
  - iii. Interventional studies (with one or more arms) of FDA-regulated drugs, biological products, or devices that meet one of the following conditions:
    - The trial has one or more sites in the United States;
    - The trial is conducted under an FDA investigational new drug (“IND”) application or investigational device exemption (“IDE”); and/or
    - The trial involves a drug, biologic, or device that is manufactured in the United States or its territories and is exported for research.
- b. Registration Exclusions: Pursuant to the FDAAA, the following is a nonexclusive listing of types of trials that are generally excluded from required registration and submission of results; however, registration of such studies and study results may be voluntarily submitted to ClinicalTrials.gov:<sup>3</sup>
- i. Phase 1 drug trials, including studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes;<sup>4</sup>
  - ii. Small clinical trials to determine the feasibility of a device or a clinical trial to test prototype devices, where the primary outcome measure relates to feasibility and not to health outcomes;<sup>5</sup>
  - iii. Trials that do not include drugs, biologics, or devices (such as behavioral interventions);<sup>6</sup>

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<sup>2</sup> For more detailed information, see “Which Trials Require Registration and Submission of Results to ClinicalTrials.gov?” at [FDAAA 801 Requirements](#), [Elaboration of Definitions of Responsible Party and Applicable Clinical Trial](#), [Registration at Clinical Trials.gov: As Required by Public Law 110- 85, Title VII](#), and [Guidance \[from NIH Office of Extramural Research\] on New Law \(Public Law 110-85\) Enacted to Expand the Scope of ClinicalTrials.gov Registration](#).

<sup>3</sup> For more detailed information, see the “Exclusions” section of [FDAAA 801 Requirements](#).

<sup>4</sup> If funded by NIH pursuant to a request for funding submitted on or after January 18, 2017, such trials require registration and results submission.

<sup>5</sup> If funded by NIH pursuant to a request for funding submitted on or after January 18, 2017, such trials require registration and results submission.

<sup>6</sup> If funded by NIH pursuant to a request for funding submitted on or after January 18, 2017, such trials require registration and results submission.

- iv. Non-interventional (observational) clinical research (such as cohort or case-control studies);
  - Although observational studies are not required to be registered, [clinicaltrials.gov](http://clinicaltrials.gov) encourages registration and results reporting of observational studies. Additionally, some journals, sponsors, and international organizations, such as the European Medicines Agency (EMA) require registration and results reporting of observational trials.
  - ClinicalTrials.gov defines Observational Studies as follows: “In an observational study, investigators assess health outcomes in groups of participants according to a research plan or protocol. Participants may receive interventions (which can include medical products such as drugs or devices) or procedures as part of their routine medical care, but participants are not assigned to specific interventions by the investigator (as in a clinical trial). For example, investigators may observe a group of older adults to learn more about the effects of different lifestyles on cardiac health.”<sup>7</sup>
- v. Trials that were ongoing as of September 27, 2007, and reached the Completion Date before December 26, 2007;
  - “[Completion Date](#)” is defined in the FDAAA as “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”
- vi. For Applicable Clinical Trials that include a device not previously approved or cleared by FDA for any use and that need to be registered, full posting of the trial information on ClinicalTrials.gov can be delayed until after the device has been approved or cleared.<sup>8</sup>
- vii. Even if your trial fits one of the exclusions from registration requirements listed above:
  - Consult the “instructions to authors” for journals in which you hope to publish to ensure that you will not be prohibited from publication in a journal because of the journal’s registration requirements.
  - Review the contractual agreement with the trial sponsor to ensure that the sponsor does not require registration and results submission.
- c. **NIH Requirements for Applicants for Grant Funding:** NIH grantees must certify compliance with FDAAA 801 in their competing applications and noncompeting continuation progress reports for any NIH grant that supports a clinical trial, even if

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<sup>7</sup> For more detailed information about observational studies, see [Observational Studies](#) and [Registration of Observational Studies](#).

<sup>8</sup> For more detailed information, see [Delayed Posting Data Element](#) and “Which Trials Must Be Registered and Have Results Submitted to ClinicalTrials.gov?” at [FDAAA 801 Requirements](#).

the grantee is not the [Responsible Party](#) for registering trials and submitting trial results to ClinicalTrials.gov.<sup>9</sup>

**d. FDAAA Definitions:**

***Applicable Clinical Trial*** is defined in 42 CFR 11. 10

Determination of Applicable Clinical Trial initiated on or after Jan 18, 2017:

- Study Type = Interventional
- Studies a US FDA regulated drug product OR a US FDA regulated device product
- Study Phase  $\neq$  Phase 1 (drug and biologic products) OR Primary Purpose  $\neq$  Device feasibility (device products)
- Any of the following apply:
  - Facility location: Country = US (or US territory)
  - US FDA IND or IDE Number = yes
  - Product manufactured in and exported from the US

***Applicable Device Clinical Trial***

- A prospective clinical study of health outcomes comparing an intervention with a device product subject to section 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act against a control in human subjects (other than a small clinical trial to determine the feasibility of a device product, or a clinical trial to test prototype device products where the primary outcome measure relates to feasibility and not to health outcomes);
- A pediatric postmarket surveillance of a device product as required under section 522 of the Federal Food, Drug, and Cosmetic Act; or
- A clinical trial of a combination product with a device primary mode of action under 21 CFR part 3, is an applicable device clinical trial, provided that it meets all other criteria of the definition under this part.

***Applicable Drug Clinical Trial*** a controlled clinical investigation, other than a phase 1 clinical investigation of a drug product subject to section 505 of the Federal Food, Drug, and Cosmetic Act or a biological product subject to section 351 of the Public Health Service Act.

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<sup>9</sup> For more detailed information about compliance with FDAAA by NIH grantees, see [What NIH Grantees Need to Know About FDAAA](#).

**Responsible Party** – “(1) is responsible for conducting the trial, (2) has access to and control over the data from the clinical trial, (3) has the right to publish the results of the trial, and (4) has the ability to meet all of the requirements FDAAA for the submission of clinical trial information”

**Sponsor** - Name of primary organization that oversees implementation of study and is responsible for data analysis. For applicable clinical trials, sponsor is defined in 21 CFR 50.3.

2. **Centers for Medicare & Medicaid Services (CMS) Billing Rule**

- a. When a trial is registered in ClinicalTrials.gov, ClinicalTrials.gov assigns the trial a National Clinical Trial Number (“NCT#”).
- b. Effective January 1, 2014, CMS requires mandatory reporting of the NCT# on claims for items and services provided in “qualified clinical trials” for Medicare coverage.<sup>11</sup>
- c. **“Qualified Clinical Trial”**:<sup>11</sup>
  - i. Purpose of trial must be the evaluation of an item/service that falls within Medicare benefit category (e.g. physicians’ service, durable medical equipment, diagnostic test)
  - ii. Trial must have therapeutic intent
  - iii. Trial must enroll patients with diagnosed disease and not only healthy volunteers

3. **NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information (“NIH Policy”)**:

**Determining what trials to register and report – see NIH’s definition of a Clinical Trial <https://grants.nih.gov/policy/clinical-trials/definition.htm>**

Use the following four questions to determine the difference between a clinical study and a clinical trial:

- 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?

Note that if the answers to the 4 questions are yes, your study meets the NIH definition of a clinical trial, even if...



- You are studying healthy participants
  - Your study does not have a comparison group (e.g., placebo or control)
  - Your study is only designed to assess the pharmacokinetics, safety, and/or maximum tolerated dose of an investigational drug
  - Your study is utilizing a behavioral intervention
- a. **Registration Requirements and Results Submission Requirements:**
- i. All clinical trials, regardless of study phase or type of intervention, that are funded by grant applications, contracts, or other transactions submitted to NIH on or after January 18, 2017, must register and report results with ClinicalTrials.gov.
  - ii. The NIH Policy’s definition of “clinical trials” is more expansive than the FDAAA’s definition of an Applicable Clinical Trial.
  - iii. The [NIH Policy](#) defines a clinical trial as “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.”<sup>10</sup> For example:<sup>11</sup>
    - Phase I clinical trials of an FDA regulated product
    - Trials of interventions not regulated by the FDA, including surgical and/or behavioral interventions
    - Small feasibility studies of devices
    - Pilot trials designed to examine the feasibility of an approach.
  - iv. Awardees undertaking clinical trials covered by the NIH Policy must ensure that the submission and updating of the same type of registration and results information, and in the same timeframes, as Responsible Parties whose trials are subject to the [Final Rule](#).<sup>12</sup>

Use the following

b. **Registration and Results Submission Exclusions:**

- i. Under the [NIH Policy](#), the following trials are not subject to mandatory registration and submission of results:<sup>13</sup>

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<sup>10</sup> Source: [NIH Definition of Clinical Trial](#)

<sup>11</sup> Source: [NIH Policy](#) pp. 4 and 21-22

<sup>12</sup> On September 16, 2016, the Public Health Service issued a “Final Rule,” [45 CFR Part 11](#), expanding the requirements for submitting registration and results information for “Applicable Clinical Trials”. The Final Rule has an effective date of January 18, 2017. Responsible Parties will have 90 calendar days (until April 19, 2017) after the effective date to come into compliance with the requirements of the Final Rule. \*ISMMS will issue a policy and accompanying training materials to reflect the revisions of the Final Rule. A Summary of the Final Rule is available at <https://www.nih.gov/news-events/summary-hhs-nih-initiatives-enhance-availability-clinical-trial-information>.

<sup>13</sup> Source: [NIH Policy](#) pp. 16 and 22

- A clinical trial sponsored by NIH and awarded before January 18, 2017, where the clinical trial does not meet the FDAAA’s definition of Applicable Clinical Trial.
  - A clinical trial that uses NIH-supported infrastructure but does not receive NIH funds to support conducting the clinical trial, where the trial does not meet the FDAAA’s definition of Applicable Clinical Trial.
- ii. However, NIH encourages researchers to register and submit results with ClinicalTrials.gov for all types of trials.
- c. **Requirements for Applicants for NIH Grant Funding:**
- i. Effective January 18, 2017, applications for NIH funding for any clinical trial are subject to the NIH Policy and must include as part of the application a plan for registering trials and submitting results to ClinicalTrials.gov.
  - ii. The NIH policy applies to applications to NIH for funding for all clinical trials. Such funding applications grant applications, “other transactions”, and contracts.
  - iii. The NIH Policy applies to all clinical trials funded in whole or part by NIH, whether or not the trial is subject to the FDAAA.
4. **ICMJE:**
- a. **Registration Requirements:** The policy of the International Council of Medical Journal Editors (ICJME) requires the registration of all prospective clinical studies in a World Health Organization-approved primary registry such as ClinicalTrials.gov.<sup>14</sup> Some journals have additional specifications for which studies must be registered. Please consult the instructions to authors for the journals in which you hope to publish the results of your trial to avoid a prohibition from being able to publish in a particular journal due to the journal’s registration requirements.
  - b. ICJME policy does not require, but encourages, reporting of clinical trial results in ClinicalTrials.gov.

**C. Which entity of the Mount Sinai Health System is the registrant of studies in CT.gov?**

As of March 1, 2017, all new registrations on ClinicalTrials.gov are registered under the Icahn School of Medicine account. This includes cases where the School faculty member also works at Mount Sinai Beth Israel, St. Luke’s, West, New York Eye and Ear, The Mount Sinai Hospital, and when applicable Mount Sinai Brooklyn and Queens. For existing records,

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<sup>14</sup> For more detailed information, see the ICJME Editorial, [“Is This Clinical Trial Fully Registered? — A Statement from the International Committee of Medical Journal Editors.”](#)

prior to March 1, 2017, where one of these Hospitals was the Institutional Registrant and the study is ongoing, the record will be transferred to the School on a case-by case basis.

#### **D. Who is Responsible for Registering Trials and Submitting Results? (What is the PIs role at ISMMS?)**

MSHS Principal Investigators (PIs) are responsible for determining whether or not they are obligated to register a trial and for any subsequent required updates including results reporting, in accordance with [Section 801 of the Food and Drug Administration Amendments Act \(FDAAA 801\)](#) and NIH 42 CFR part 11. See “Checklist for Evaluating Whether a Clinical Trial or Study requires registration in ClinicalTrials.gov” attached Appendix A.

1. The FDAAA requires the “Responsible Party” to register and submit results of an Applicable Clinical Trial. The Responsible Party is defined as:<sup>15</sup>
  - a. The sponsor of the clinical trial, or
  - b. The principal investigator (PI) of such clinical trial if so designated by a sponsor, grantee, contractor, or awardee, if: 1) the PI is responsible for conducting the trial, 2) the PI has access to and control over the data from the clinical trial, 3) the PI has the right to publish the results of the trial, and 4) the PI has the ability to meet all of FDAAA's requirements for the submission of clinical trial information.
2. If a trial is being conducted under an IND or IDE, then the IND/IDE holder is the Responsible Party, regardless of how the trial is funded.<sup>16</sup>
  - a. If the IND/IDE is issued in the name of the PI, the PI is the Responsible Party.
  - b. If the IND/IDE is issued in the name of the sponsor of the research, the sponsor of the research is the Responsible Party.
3. For trials not conducted under an IND or IDE at ISMMS:

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<sup>15</sup> For more detailed information regarding “Responsible Party” and “Sponsor,” see [Elaboration of Definitions of Responsible Party and Applicable Clinical Trial](#) and [Responsible Party data element](#).

<sup>16</sup> For more detailed information, see [ClinicalTrials.gov: Requirements and Implementation Strategies](#) and [Identifying the "Responsible Party" under FDAAA for Applicable Clinical Trials Conducted Under NIH Grants](#).

- a. Contractual agreements with industry/pharmaceutical sponsors of trials typically designate the industry/pharmaceutical sponsor as the Responsible Party.
  - b. Government (federal and state) funded grants designate the grant recipient, ISMMS, as the Responsible Party. **However, ISMMS delegates this responsibility to the PI, making the PI the Responsible Party.**
  - c. Where no external funding exists for the trial, the PI is the Responsible Party by default.
4. Exceptions exist. Check the agreement/contract with the sponsor (or the grant's terms and conditions) regarding who is responsible for trial registration and results submission to ClinicalTrials.gov. ISMMS Grants & Contracts Office can assist with providing a copy of the agreement/contract/grant if needed.
  5. If it is unclear who is responsible for registering an applicable clinical trial, investigators should consult with the sponsor, funding agency, and/or other study investigators to define who the responsible party will be.
6. If the Responsible Party (RP) leaves ISMMS
    - a. If the study is on-going, and the RP plans to transfer the study they must notify the [ORS](#) prior to leaving ISMMS to initiate transfer of the record to the new institution.
    - b. If the RP plans to complete the study or terminate the study, they must contact the [ORS](#) to close the study on CT.gov prior to leaving ISMMS.
  7. If the Responsible Party (RP) and/or their designee are unavailable due to unexpected events, the Chair of the department will assign someone from the department as the new RP of the study or assume the role themselves.

## **E. When Must A Trial Be Registered?**

1. **FDAAA and NIH Policy:** The Responsible Party (that is, the sponsor or designated PI) must register the trial **no later than 21 days after enrollment of the first subject.**<sup>17</sup>

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<sup>17</sup> Source: [FDAAA 801 Requirements](#); [NIH Policy](#) p. 21

2. **ICJME Compliance:** The ICJME requires registration **before the first subject is enrolled**.<sup>18</sup>
  - a. The ICMJE will accept registration in any of the World Health Organization-approved primary registries, including ClinicalTrials.gov. However, registering the trial with ClinicalTrials.gov fulfills both the regulatory and ICMJE criteria for registration.
  - b. The ICMJE does not define the timing of “before the first subject is enrolled”, but best practice is considered that registration should be completed before a subject is consented for a trial.
  
3. **Required Registration Updates:**
  - a. Responsible Parties should update their records within 30 days of a change to any of the following:
    - i. [Recruitment Status](#)
    - ii. [Overall Recruitment Status](#)
    - iii. [Completion Date](#)
  - b. Other changes or updates to the record must be made at least every 12 months. It is recommended that the Record Verification Date be updated at least every 12 months for studies that are not yet completed, even if there were no changes to the record.
  - c. See “Role of Office of Research Services” (ORS) for details on updating study information.
  
4. **Is IRB Approval Required before registering a study with clinicaltrials.gov?**
  - a. In accordance with guidance from the Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA), the clinical trial listing does not require IRB approval if the “Overall Recruitment Status” of the study is “Not yet recruiting.”
  - b. IRB approval is required before recruitment of study subjects begins, as subject recruitment is considered to be part of the informed consent and subject selection process.

## **F. When Must Results Be Reported?**

1. **FDAAA and NIH Policy:** Clinical trial results, including adverse events, must be reported within **12 months** after the trial’s [Completion Date](#), which is defined as “the

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<sup>18</sup> Source: [ICMJE – Clinical Trial Registration](#)

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". Reporting of Results must occur even when a protocol is terminated earlier than initially planned.<sup>19</sup>

2. **ICJME Compliance:** The ICMJE encourages posting of clinical trial results in clinical trial registries *but does not require it*. The ICMJE does not consider as "prior publication" the posting of trial results in ClinicalTrials.gov if results are limited to a brief (500 words or less) structured abstract or tables that include subjects enrolled, key outcomes, and adverse events.

3. **When is Delayed Submission of Results Permitted?**

a. **Certification:** The [Responsible Party](#) may delay the submission of results until the deadlines described below by submitting a certification to clinicaltrials.gov that an Applicable Clinical Trial meets either of the following conditions:

i. The trial reached its [Completion Date](#) before the drug, biologic, or device is initially approved, licensed, or cleared by FDA for any use (referred to on ClinicalTrials.gov as "certify initial approval").

- **Results deadline:** No later than 30 days after the drug or device is approved, licensed or cleared by the FDA

ii. The trial studies a new use of an FDA-approved drug, biologic, or device (that is, a use not included in the labeling), and the manufacturer of the drug, biologic, or device is the sponsor of the trial and has filed or will file within 1 year an application to FDA for approval or clearance of that use (referred to on ClinicalTrials.gov as "certify new use").

- **Results deadline:** The earlier of the date that is 30 days after the date that:

- The new use of the drug or device is approved, licensed, or cleared by FDA; FDA issues a letter for the new use of the drug or device, such as a complete response letter; and the application or premarket notification for the new use is withdrawn without resubmission for no less than 210 days; or
- 2 years after the date a certification is submitted, if none of the events listed above has occurred.

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<sup>19</sup> Source: [FDAAA 801 Requirements](#); [NIH Policy](#) p. 21

- iii. Note: If a Responsible Party that is both the sponsor and the manufacturer submits a new use certification, this certification must be made with respect to each Applicable Clinical Trial that is required to be submitted in an application or report for licensure, approval, or clearance of the use studied in the clinical trial.
  - iv. Submit certifications for delayed results within ClinicalTrials.gov. After logging into the study in ClinicalTrials.gov, proceed to the “Delay Results” link in the “Results Section” of the Record Summary for the study in ClinicalTrials.gov.<sup>20</sup>
- b. **Delayed Submission of Results:** Reporting of results can be delayed beyond the 12-month required timeline if:
- i. The trial is of a drug or device that has not been approved for marketing by the FDA for any indication, in which case result reporting will be required within 30 days of initial approval by the FDA;
  - ii. The trial is of a drug or device for which the manufacturer has filed or is preparing to file an application seeking approval of the new use studied in the trial, in which case result reporting will be required within 30 days of initial approval by the FDA; or
  - iii. A request for a delay that “demonstrates good cause” has been granted by the Director of the NIH.

## **G. Additional Requirements: FDA and Informed Consent**

### **1. FDA:**

- a. A completed Form FDA 3674 - Certification of Compliance indicating that the requirements of FDAAA 801 have been met for the following applications and submissions to the FDA for a drug, biological product, or device:<sup>21</sup>
  - i. Investigational New Drug Application (IND)
  - ii. New Clinical Protocol Submitted to an IND
  - iii. New Drug Application (NDA)
  - iv. Efficacy Supplement to an Approved NDA

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<sup>20</sup> For more detailed information of delayed results submission, see slides 19-23 of [Overview of FDAAA and Other Trial Registration Policies](#).

<sup>21</sup> For detailed information, see [Instructions for Completion of Form FDA 3674 – Certification of Compliance](#); [FDA Regulatory Guidance as to Form FDA 3674](#); and [FDA’s Role in ClinicalTrials.gov Information](#)

- v. Biologics License Application (BLA)
  - vi. Efficacy Supplement to an Approved BLA
  - vii. Abbreviated New Drug Application (ANDA)
  - viii. Premarket Approval Application (PMA)
  - ix. PMA Panel Track Supplement
  - x. Humanitarian Device Exemption (HDE)
  - xi. 510(k) submissions that refer to, relate to, or include information on a clinical trial
- b. Note – FDA does not require the submission of a Form FDA 3674 with an Investigational Device Exemption (IDE) application.

## 2. Informed Consent:

- a. **FDAAA:** Pursuant to [FDA Guidance](#), the following exact statement must be included in the informed consent documents of Applicable Clinical Trials:<sup>22</sup>

“Basic information about this study will appear on the website <http://www.ClinicalTrials.gov>. There are a few reasons for this: the National Institutes of Health (NIH) encourages all researchers to post their research; some medical journals only accept articles if the research was posted on the website; and, for research studies the U.S. Food and Drug Administration (FDA) calls "applicable clinical trials" 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.”

Or go to the **PPHS** - the required CT.gov language should be in the Informed Consent provided in the [Informed Consent Form Template](#).

- b. **NIH Policy:** Informed consent documents for clinical trials funded by NIH must include a specific statement relating to the posting of clinical trial information with [ClinicalTrials.gov](http://www.ClinicalTrials.gov).<sup>23</sup>

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<sup>22</sup> For detailed information, see FDA Regulatory Guidance at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM291085.pdf>.

<sup>23</sup> Source: [NIH Policy](#) p. 23



## **H. Role of ISMMS Office of Research Services (ORS)**

The Office of Research Services as part of the Dean's Office and the ISMMS CTSA, facilitates registration and reporting for MSHS researchers.

ORS is **not** the Responsible Party (RP).

The ORS provides support to RPs in the initial registration and maintenance in CT.gov:

1. Overall administration of the CT.gov system for ISMMS
  - a. Oversight of the Protocol Registration System (PRS)
  - b. Account creation for PIs
  - c. Monitors and notifies PIs if their study no longer meets compliance
  - d. Assists RPs with registration & updates of trials
  - e. Assists PIs with input of results
  
2. Facilitate transfers of records for PI's studies
  - a. Transfer of record from another institution to ISMMS – If a PI is coming to ISMMS and will be implementing the study (obtaining IRB approval and enrolling subjects at ISMMS).
  - b. Transfer of record from ISMMS to another institution – If a PI is leaving ISMMS for another institution and will be conducting the study at new institution.  
(Note: if a PI leaves ISMMS and will be closing the study, must complete record information on CT.gov including posting results if applicable.)

## **L How to request ORS assistance with registration and reporting**

Make a formal request on the ORS website:

<http://icahn.mssm.edu/research/portal/resources/office-research-services>

### 1. Office of Research Services

The Office of Research Services (ORS) serves as a central resource for the Mount Sinai Health System (MSHS) research community. ORS assists the research community with how to navigate the internal research infrastructure and external research agencies; delivers research orientation for new faculty and staff; offers consulting services, ongoing training, education, and communication support; and provides a wide range of research tools.

The ORS staff answers all categories of research questions or directs questions to the appropriate office or individual who can provide the answers to members of the research community. We offer consultation services for investigators and their teams, providing guidance on submissions to ClinicalTrials.gov, Investigational New Drug (IND), and Investigational Device Exemption (IDE). ORS also offers customized training and education to the research community.

The ORS team responds to questions from the public about research conducted at Mount Sinai.

For quick access to a menu of ORS support options, please visit the [ORS Research 411 Portal](#).

#### **Acknowledging ORS Support**

ORS receives support from the Icahn School of Medicine at Mount Sinai (ISMMS) Dean's Office and ConduITS - the Institutes for Translational Sciences.

Publications arising from any research project receiving support from ORS must adhere to the [NIH Public Access Policy](#) and should acknowledge support by stating "Supported by grant UL1TR001433 from the National Center for Advancing Translational Sciences, National Institutes of Health."

- Research 411
- Research Orientation for New Faculty and Staff
- Consulting Services
- Training, Education, and Communications

- ▶ Research 411 Portal
- ▶ Research Administration Offices

#### **Office of Research Services**

[Meet Our Team](#)

[Toolkit and Policies](#)

[External Research Resources](#)

[Research Subject Recruitment](#)

#### **Contact Us**

##### **Office of Research Services (ORS)**

Icahn School of Medicine at Mount Sinai

Tel: 212-824-7294

Fax: 917-265-8297

[research.services@mssm.edu](mailto:research.services@mssm.edu)

[One Gustave L. Levy Place](#)

[Box 1120](#)

[New York, NY 10029](#)

The Icahn School of Medicine at Mount Sinai (ISMMS) Dean's Office and ConduITS - the Institutes for

2.

**Research Orientation for New Faculty and Staff**

**Consulting Services**

Create a login with the [ORS Help Center](#) to request consulting services. Select from the following options:

- **ClinicalTrials.gov registration and maintenance assistance**
- Pre-protocol development consultation
- Investigational Device Exemption (IDE) consulting
- Investigational New Drug (IND) applications consulting. If you need assistance with emergency use of an investigational drug or biologic, contact Ivy Cohen of the Investigational Drug Services (IDS) at 646-763-1889 to discuss your situation.
- ResearchMatch.Org support (Select ResearchMatch.org assistance in the dropdown menu)
- Research subject recruitment and retention consulting

**Training, Education, and Communications**

Icahn School of Medicine at Mount Sinai  
Tel: 212-824-7294  
Fax: 917-265-8297  
[research.services@mssm.edu](mailto:research.services@mssm.edu)

One Gustave L. Levy Place  
Box 1120  
New York, NY 10029

The Icahn School of Medicine at Mount Sinai (ISMMS) Dean's Office and ConduITS - the Institutes for Translational Sciences support ORS. (CTSA grant #UL1TR001433)

3.

Help Center / Office of Research Services  
**ClinicalTrial.gov Assistance**

Raise this request on behalf of

Summary

- None
- Registration
- Update
- Posting Results
- Other**
- None

Select the type of number to identify your project:

## **How do I obtain an account with ClinicalTrials.gov in order to register a Trial and Submit Results?**

ISMMS has an organizational account with ClinicalTrials.gov. Registration is completed through the menu-driven Protocol Registration System (“PRS”). Since ISMMS has a PRS Administrator, when registering with ClinicalTrials.gov contact the [ORS](#) for assistance with this.

For studies that require the PI to release data to CT.gov, and therefore an account is required, the ISMMS PRS Administrator will have already assigned that PI a username and password. If you have any questions regarding your account and/or the release of data please contact the [ORS](#)

## **When Should a Trial be registered?**

### **Timeline**

ClinicalTrials.gov requires clinical trial information to be submitted no later than 21 days after enrollment of the first participant.

ICMJE requires trials to be registered before enrollment of the first participant.

Clinicaltrials.gov QA committee reviews all registrations prior to making the study viewable to the public on their website. The review process usually takes 2-5 business days and they may request clarifications before providing an NCT number which indicates trial is registered.

### **Posting Results for a Study**

Results are required to be posted within one year of the Primary completion date. Primary completion date is defined as the date of the last study visit or data is collected for the primary outcome measure. The results required, but are not limited to, participant flow, demographic and baseline characteristics, outcomes and statistical analyses, and adverse events.

A copy of the protocol, including all amendments and the statistical analysis plan, if not included in protocol are required to be submitted at time of results posting.

### **Quality Control**

RP must correct or address review comments by the QC review process:

- Within 15 calendar days for clinical trial registration information

- Within 25 calendar days for clinical trial results information

#### Changes

- Within 30 days for changes with the completion date or to the protocol
- Within 30 days for changes with the completion date

## **J. Enforcement of Reporting Requirements**

### **Internal to ISMMS:**

The RP is responsible for registration, updates and reporting to ClinicalTrials.gov.

ORS will monitor studies requiring annual updates, reporting and other compliance requirements. PIs and study teams will be notified via the ORS ticketing system when there are outdated progress and final reports due. ORS provides this as a service, and is not accountable to ensure that compliance is met.

The responsible party is accountable to meet compliance requirements. Chairs of each department will be notified regarding studies of PIs in their department that are delinquent in meeting approaching compliance requirements and deadlines.

The department of the PIs that do not meet the compliance deadline and therefore incur penalties as listed below will be held accountable for all financial penalties that ISMMS receives. Civil and criminal penalties apply directly to the responsible party listed on the study.

### **Federal Penalties:**

- FDAAA Final Rule – Possible criminal proceedings and civil penalties of \$11,569/per study /day); Loss of HHS funding (issued in 2018)
- ICMJE – Refusal to publish (Effective in 2005)
- Final NIH Policy – Loss of NIH funding to PI, which can extend to Mount Sinai (issued in 2016)
- FDA – Civil or criminal judicial actions for prohibited acts
  - Failure to submit a certification required by 402(j)(5)(B) of the PHS Act or knowingly submitting a false certification
  - Failure to submit clinical trial information

- Submission of clinical trial information which is false or misleading in any particular

## Appendix A

### Checklist for Evaluating Whether a Clinical Trial or Study requires registration in Clinicaltrials.gov.

For more detailed instructions please go to **page 2** of the following link:

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

**NOTE:** MSHS Principal Investigators (PIs) are responsible for determining whether or not they are obligated to register and for any subsequent required updates including results reporting, in accordance with [Section 801 of the Food and Drug Administration Amendments Act \(FDAAA 801\)](#) and NIH 42 CFR part 11.

Question			
Is this study fully or partially funded by the National Institutes of Health (NIH)?	<input type="checkbox"/> Yes <input type="checkbox"/> No	If YES, register your study in CT.gov.  If NO, continue.	Registration required within 21 days of first enrollment.  Email <a href="mailto:research.services@mssm.edu">research.services@mssm.edu</a>
Are you planning to submit results to a journal for publication?	<input type="checkbox"/> Yes <input type="checkbox"/> No	If YES, contact the journals you plan to submit to for publication for their requirements for CT.gov registration.  If the journal does NOT require registration, you must continue with the below questions to evaluate if your study is an applicable clinical trial (ACT) which will require registration.	Registration required prior to first enrolled research subject.  Email <a href="mailto:research.services@mssm.edu">research.services@mssm.edu</a>
<b>If "Yes" is answered to all 4 questions below, and the study was initiated on or after January 18, 2017, the trial would meet the definition of an applicable clinical trial (ACT) that is required to be registered under 42 CFR 11.22.</b>			
Is the study interventional (a clinical trial)?			Registration required within 21

Study Type data element is “Interventional”	<input type="checkbox"/> Yes <input type="checkbox"/> No	days of first enrollment.
<p>Does the study evaluate at least one drug, biological, or device product regulated by the United States Food and Drug Administration (U.S. FDA)?</p> <ul style="list-style-type: none"> <li>• <i>Studies a U.S. FDA-regulated Device Product data element is “Yes” and/or</i></li> <li>• <i>Studies a U.S. FDA-regulated Drug Product data element is “Yes.”</i></li> </ul>	<input type="checkbox"/> Yes <input type="checkbox"/> No	Email <a href="mailto:research.services@mssm.edu">research.services@mssm.edu</a>
<p>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?</p> <ul style="list-style-type: none"> <li>• <i>For drug product trials, Study Phase data element is NOT “Phase 1” and</i></li> <li>• <i>For device product trials, Primary Purpose is NOT “Device Feasibility.”</i></li> </ul>	<input type="checkbox"/> Yes <input type="checkbox"/> No	
<p>Do ANY of the following apply (is the answer “Yes” to at least one of the following sub-questions: 4a, 4b, OR 4c)?</p> <p>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.</p> <p>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.”</p> <p>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.”</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No	