ClinicalTrials.gov Registration Guide

The Food and Drug Administration Amendments Act (FDAAA), National Institutes of Health (NIH) and International Committee of Medical Journal Editors (ICMJE) require registration of certain clinical trials. If a study meets FDA, NIH or ICMJE registration criteria, it must be registered on a publicly accessible website (ClinicalTrials.gov). Meeting FDAAA requirements satisfies federal regulations. Meeting ICMJE requirements satisfies one of a journal's condition for publishing.

This guide is a resource for KUMC faculty and staff. The guide covers registering new studies and maintaining compliance with site requirements until the study is completed. This guide reflects the HHS final rule and NIH complimentary policy released in September 2016 on study registration and results reporting. The final rule and policy went into effect on January 18, 2017. Enforcement by the FDA and NIH began April 18, 2017.

Guide Contents

What is an "Applicable Clinical Trial (ACT)"?

An APPLICABLE CLINICAL TRIAL is the term used in Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) to designate the scope of trials that may be subject to the registration and reporting requirements in FDAAA.

Generally speaking, if the study meets the following criteria, it is an ACT:

1. Involves a drug or device subject to FDA regulation
2. Not a phase I (drug) or small feasibility (device) study
3. Involves at least one site in the US

For the complete statutory definition of an ACT and an elaboration on the FDA's current thinking, see http://prsinfo.clinicaltrials.gov/ElaborationsOnDefinitions.pdf

For an NIH flowchart to help you identify an ACT according to FDAAA requirements, see: https://grants.nih.gov/clinicaltrials_fdaaa/docs/Flow_chart-ACT_only.pdf

Overview of Differences between ICMJE and FDAAA

Below is an abbreviated breakdown of the requirements by each authority. For Investigator-initiated research, pay close attention to ICMJE guidelines. Studies that do not meet FDAAA requirements, and are not NIH funded, may meet ICMJE requirements. ICMJE requirements include a broad group of studies.

Trial Registration Requirements by Authority[1]

	ICMJE (effective 2005)	FDAAA (issued 2007) and HHS Rule (Sept. 2016)	NIH Complimentary Policy (issued Sept. 2016)
What sections must be created and managed in clinicaltrials.gov?	Study registration	Study registration and results reporting	Study registration and results reporting
What phase meets requirements?	Any	Not phase I (drugs); Not small feasibility trial (devices)	Any
What intervention type[2] meets requirements?	Any	Drug, biologic, and devices regulated by the FDA	Any
Funding source	Any	Any	NIH[5]
When to register the trial?	PRIOR to enrollment of first subject	Within 21 days of enrollment of first subject	Within 21 days of enrollment of first subject
When to report results?[3]	Not Applicable	Within 12 months of final data collection for the primary outcome[4]	Within 12 months of final data collection for the primary outcome[4]
Potential Enforcement Action	Refusal to publish	Criminal proceedings and civil penalties (up to	NIH funding withheld

		$10,000/day); DHHS funding withheld	

1. Table adapted from a presentation: Zarin, Deborah, Williams, Rebecca, (September 27, 2016) *final Rule for Section 801 of the Food and Drug Administration Amendments Act of 2007 (42 CFR Part 11), Final Rule Webinar Series – 1 of 3* [PowerPoint slides]
2. Intervention types include: drugs, surgical procedures, devices, behavioral treatments, dietary interventions, quality improvement interventions, and process-of-care changes
3. Deadline to submit results to Clinicaltrials.gov is INDEPENDENT of publication status
4. Trials considered as *Applicable Clinical Trials* by FDAAA are required to submit results to Clinicaltrials.gov
5. Clinical trials that use NIH-supported infrastructure, but receive no other NIH funds for the conduct of a specific clinical trial are not subject to the NIH Policy.

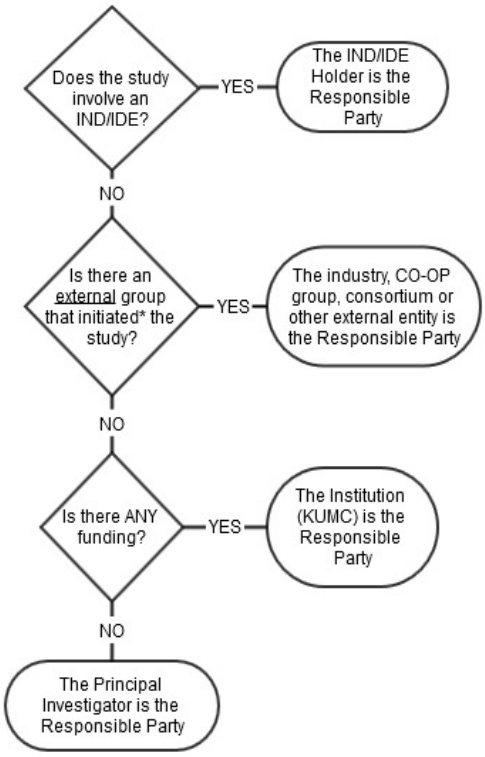
A note regarding results registration:

- Primary Completion Date: results for the primary outcome are due 12 months after the Primary completion date, as indicated in the study registration.
- Secondary Completion Date: data collection for secondary outcomes often continues on after final data collection for the Primary outcome measure. In these situations, results data for remaining secondary outcomes are due within 12 months of the Study completion date, as indicated in the study registration.

Who Registers the Study on Clinicaltrials.gov?

The "Responsible Party" refers to the entity or individual who is responsible for registering a trial in a clinical trial registry data bank (i.e. ClinicalTrials.gov). They are the ONLY user who is able to "release" the initial record and future updates to it for public view. They are responsible for ensuring the study registration stays accurate and up-to-date. There is ONE responsible party per study registration. This is to prevent a study from being registered multiple times.

Determining the Responsible Party



When the IND/IDE holder is a KUMC Investigator, they are listed as the Responsible Party

The external group is the entity that writes the protocol or funded the protocol to be written

If there is no IND/IDE, and the study is initiated by a KUMC Investigator, then KUMC or the Investigator will be listed as the Responsible Party. For ACTs where there is no IND or IDE, the funding recipient is generally considered to be the sponsor and therefore the responsible party. For NIH grants, the funding recipient is the grantee institution, not the PI on the grant. If the Investigator is designated as the Responsible Party, they will be notified and marked as such in clinicaltrials.gov.

NIH Funded Studies

The NIH requires registration and results reporting for all NIH-funded clinical trials, regardless of whether or not they are subject to FDAAA (http://grants.nih.gov/clinicaltrials_fdaaa/at-a-glance.htm). How does the NIH define a clinical trial? Ask the following four questions, and if the answer is yes to all four, then the NIH considers the research 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 that will be evaluated a health-related biomedical or behavioral outcome?

All competing applications (new and renewal) and progress reports for NIH grants (including cooperative agreements) supporting ACTs must include a certification of compliance with FDAAA. This includes applications where the trial has not yet begun (e.g. is proposed) or is not yet required to be registered (e.g. less than 21 days since first subject was enrolled), as well as applications and progress reports that include an on-going trial that is already registered in ClinicalTrials.gov.

For details on how to certify compliance to NIH, see: http://grants.nih.gov/ClinicalTrials_fdaaa/certify-compliance.htm

A breakdown of steps and details on each to ensure compliance with NIH implementation of FDAAA is available at: http://grants.nih.gov/ClinicalTrials_fdaaa/steps.htm

Potential Consequences Resulting from Non-Compliance

The Responsible Party is accountable for the accuracy and completeness of the study registration. Complying with updating registrations and providing study data according to requirements will prevent any of the following actions. Non-compliance with FDAAA and ICMJE requirements can have serious consequences.

ICMJE Enforcement Actions (individual journals):

1. Journal does not accept article on the study for publication

FDAAA Enforcement Actions:

1. Notification from Clinicaltrials.gov when records are out of compliance
2. Monetary penalty of up to $10,000/day per instance of non-compliance
3. DHHS funding withheld

NIH Enforcement Actions:

1. NIH funding withheld

CMS Billing Requirement

The National Clinical Trial (NCT) ID number (assigned once initials registration is approved by clinicaltrials.gov) is required for all qualified claims. The Centers for Medicare and Medicaid Services initiated requirement on January 1, 2014. Any claim that does not include the NCT will not be paid and will be returned. The NCT ID must be available before any qualified claim is submitted.

The NCT ID for each study is stored in Velos (aka CRIS). KU Hospital billing has access to study records in CRIS to obtain the number. If a trial does not meet any registration criteria (i.e. chart reviews), NCT00000000 is entered into CRIS to denote the study is not registered.

Accessing Clinicaltrials.gov

You need an account in order to access the Clinicaltrials.gov Protocol Registration System (PRS). PRS administrators at KUMC are part of the Clinical Research Administration (CRA) within the KUMC Research Institute and Cancer Center Clinical Trials Office. A PRS administrator will create an account for you under the KUMC organizational account.

Requesting a ClinicalTrials.gov Account:

- Contact Melissa Willer (mwiller@kumc.edu) in the KUMC RI CRA for a new account.
    a. For studies running through the Cancer Center Regulatory Office, contact your project manager in that office for more information.
- KUMC has an established Institutional account for all KUMC investigators/faculty
    - Do not request an Individual Account or another Organizational Account through Clinicaltrials.gov

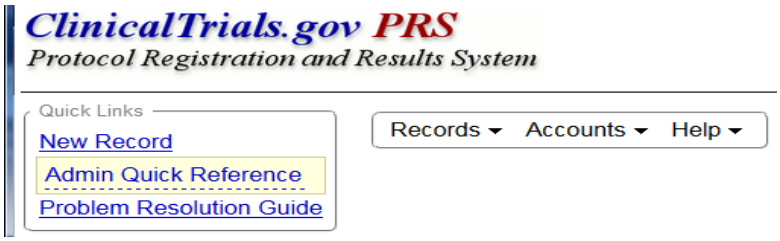
Logging in to the Protocol Registration System (PRS):

After your account is created, you will receive an email from ClinicalTrials.gov with your username and a temporary password. Click on the link in the email to go to the ClinicalTrials.gov PRS log-in page (**https://register.clinicaltrials.gov/**)

Logon Details: Organization: **UKansasMCRI**
User Name: *as it is assigned to you in your notice from PRS*
Password: *enter your temporary password*

After logging in, you will be on the "main page" of the site. Features of the main page:

1. **You will see the Quick Links section and Drop down menus (pictured below):**
    - The "Records" menu is a way for you to view a problem report for your studies. You can also quickly access CT.gov QA review comments from the list.
    - Mouse over the "Accounts" drop down list to update your account information or to change your password.
    - Mouse over the "Help" menu for guides on different clinicaltrials.gov topics.



2. **You will see a list of all records to which you have access**. Access to studies is limited to only those studies where the user is the Responsible Party or access has been designated by the PI. If you should have access to a study, and do not, contact the CRA.

3. **Access to View/Edit a Study:** Click "Open" next to the study you want to view/edit. This will take you to the Record Summary (to be discussed later) page.

4. **Create a New Study Registration:** Click "New Record" in the Quick Links section. This will start the process to add a new study to the site. See next section for preferred data and information to be entered in some of the required fields.

Study Registration

Language Used in the Study Registration

The main audience for clinicaltrials.gov is the public. Keep this in mind when creating a study registration in the system. All attempts should be made to keep the language to an 8th grade reading level. If there is an IRB approved consent form available, this serves as a good starting point. The public uses the website to learn more about clinical trials recruiting in their area. The study registration should provide an understandable and readable outline of the study to the lay person.

Preferred Format for Data Fields

Studies registered in clinicaltrials.gov follow the same registration outline. There is some variance on required fields depending on the type of study (interventional, observational or an expanded access).

Included at the end of this document is a table. The table includes some recommendations to follow when creating new study registrations in the system. Not all fields for a registration are included in the table.

Data Sharing Statement – NEW REQUIREMENT

The ICMJE requires clinical trials that begin enrolling participants on or after 1 January 2019 to include a data sharing plan in the trial's registration. Data sharing statements to satisfy ICMJE requirements must indicate whether individual participant data will be shared ("Undecided" is not an acceptable answer), and if so what data will be shared, whether additional documents will be available, when and for how long data will become available, and by what access criteria data will be shared.

Protocol Submission to Clinicaltrials.gov – NEW REQUIREMENT

As part of the HHS final rule and NIH complimentary policy, a copy of the study protocol will be required to be uploaded to clinicaltrials.gov for some studies. There is a "Document Section" for registrations. Only certain studies required documents to be uploaded. For studies that are required to upload documents, a copy of the protocol and statistical analysis plan is uploaded to this section. Studies also have the option to upload informed consent forms – this is optional for all studies.

Reviewing and Editing Study Registrations

ALL studies registered on clinicaltrials.gov must be reviewed and released periodically. These time points are critical to maintaining compliance with FDAAA regulations.

It is up to the Responsible Party of the study registration to review, revise and verify all information in the registration. Clinicaltrials.gov will NOT send a notice or reminder when review is required. **Only the Responsible Party can release information for public viewing.**

Key time points for Clinicaltrials.gov Registrations

Initial Registration: Refer to table on page 2. It is recommended to register all trials before enrollment of the first subject.

Predetermined time points when registrations require review/revision/release:

a. Change in Recruitment Status: 30 calendar days after the change in status
b. IRB Board Status: 30 calendar days after the change in status
c. Individual Site Status: 30 calendar days after the change in status

All studies need to be reviewed and released at least annually.

Results and Adverse Event Data: Enter within 12 months of the Primary Completion Date.

Response Times – NEW REQUIREMENT

Effective January 18, 2017, the Responsible Party will be required to respond to comments from Clinicaltrials.gov within a timely manner. Clinicaltrials.gov issues requests for changes or clarifications to the protocol section and results section.

- When comments are issued for the protocol section, the Responsible Party has **15** days to respond.
- When comments are issued for the results section, the Responsible Party has **25** days to respond.

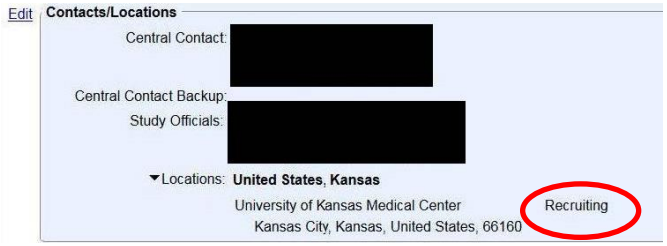
Steps to review and release the study registration

Follow these steps when it's time to review, verify and release a study registration:

1. Login to the study at register.clinicaltrials.gov
2. Click "Open" next to the registration you want to view
3. This will take you the study Record Summary page. There are three main sections on this page:
    a. **Record Status** – contains key dates for the posting; last time record was updated, last time the record was released, last public site update
    b. **Protocol Section** – location of study information used for public site posting
    c. **Results Section** – where results and adverse events for study are entered
4. To edit study information, click "Open" to the left of the "Protocol Section"
5. From the "Protocol Section" page, you can edit all parts of the study.
    a. Record Verification: Update when reviewing the record for accuracy and completeness, even if no other updated information is submitted.

Tip: When a trial's Overall Status changes to "Active, not recruiting," it is not necessary to change recruitment status for each location. Location recruitment status is only shown on ClinicalTrials.gov when Overall Status is "Recruiting".

But…when you change the Overall Status to Recruiting, you also need to update the recruiting status that is part of the Contacts/Locations section at the end of the record (pictured below).



6. After you have reviewed all study sections, and made any changes, return to the "Record Summary" page. To release the updates:
    a. First click "Complete" (the page will reload),
    b. Then "Approve" (the page will reload again),
    c. Then "Release".
        i. NOTE: If you are reviewing the study at a required time point, you will NOT be able to release the record BEFORE clicking into the "Protocol Section."
    d. After you Release the registration, the site will ask you to confirm you-are-you via a checkbox. Click the box and then release and the registration. Clinicaltrials.gov QA will review all changes before making them available to the public. For new studies and results, they may return comments. If they do, those comments must be addressed before the registration is approved.

Appendix 1: Study Registration Data Field Recommendations

Section	Field	Field Note
Study Identification	Unique Protocol ID	Include the study IRB#, i.e. STUDY12345678.
	Secondary ID	Required when the study involves NIH or other grant funding. If the study received funding from the Frontiers CTSA grant, include the following: ID = UL1TR000001 (add National Institutes of Health to Collaborators). Can also include when applicable, a registry identifier, EudraCT number, or other identifier.
Study Status	Study Start	Month/Day/Year the study starts enrollment
	Primary Completion Date	Final data collection date for primary outcome measure (Month/Day/Year; NOT when the study is *closed* with the IRB)
	Study Completion Date	Final data collection date for the study (Month/Day/Year; NOT when the study is *closed* with the IRB)
Sponsor/ Collaborators	Responsible Party	An indication of whether the responsible party is the sponsor, the sponsor-investigator, or a principal investigator designated by the sponsor to be the responsible party. Select one. ● Sponsor: The entity (for example, corporation or agency) that initiates the study ● Principal Investigator: The individual designated as responsible party by the sponsor ● Sponsor-Investigator: The individual who both initiates and conducts the study (i.e. when KUMC Investigator is IND holder)
	Collaborators	Organization(s) providing support: funding, design, implementation, data analysis or reporting. Include all collaborators on the research project. If the study is funded by the NIH, include the name of the agency.
Oversight	U.S. FDA-regulated drug	Yes/No – Does the study involve an FDA-regulated drug or biologic? Note: this is not asking if the drug is investigational.
	U.S. FDA-regulated device	Yes/No – Does the study involve an FDA-regulated device? Note: this is not asking if the drug is investigational.
	Board Information	Name: Institutional Review Board Affiliation: University of Kansas Medical Center Phone: 913-588-1240 Email: humansubjects@kumc.edu Address: Institutional Review Board, University of Kansas Medical Center, 3901 Rainbow Blvd., MS1032, Kansas City, KS 66160

	U.S. FDA IND/IDE Study	Yes/No – Yes if the study is being conducted under an IND or IDE. Answer NO if the study is being conducted under an IND exemption or did not require FDA review.
	Section 801 Clinical Trial	Section 801 Clinical Trial: Yes/No – Is the study an "applicable clinical trial"? See page 2 of this document for reference.
Study Description	Brief Summary	Short description of the protocol intended for the lay public, i.e. *"The purpose of this study is to determine…"*
Conditions	Conditions or Focus of Study	The name(s) of the disease(s) or condition(s) studied in the clinical study, or the focus of the clinical study.
Study Design	Depends on the Study Type	Complete fields based on the type of study (i.e. interventional, observational, expanded access)
Arms and Interventions	Interventions	Include all interventions that the participants will receive. This includes any investigational agents AND when applicable, standard of care treatment.
Outcome Measures	Outcomes	A concise name for the specific measure that will be used to determine the effect of the intervention(s) or, for observational studies, related to core objectives of the study and receiving the most emphasis in assessment. Describes what will be measured and not why it is measured. All primary and secondary outcome measures listed in the protocol must be included. The outcome measures listed in this section will be used for the results section.
	Time Frame	Time point when outcome measure is assessed. Each outcome measure can only have one time point. If multiple outcomes are based on the same underlying measure assessed at different time points (i.e. 8 weeks, 12 weeks and Final Visit), then each unique combination of measurement and time frame is entered as a separate outcome measure (i.e. Change from Baseline to Week 8 in MMSE/ Baseline to Week 12).
	Outcomes using a scale	The following information in the Outcome Measure Description field: ● All scale ranges (i.e., minimum and maximum scores) required to interpret any values in the data table. For example, if the *total* score is reported, the *total* range should be provided. If subscale scores are reported, the range for each subscale should be provided. ● For each scale range provided, specify which values are considered to be a better or worse outcome (i.e., Do higher values represent a better or worse outcome?). ● If subscales are combined to compute a total score, consider indicating how subscales are combined (summed, averaged, etc.).
	Example 1	Title: Systolic Blood Pressure Outcome measure description: Change in Systolic Blood Pressure

	Example 2	Title: Parkinson's Disease Questionnaire – 39 (PDQ-39) Outcome measure description: The PDQ-39 is a measure of quality of life in Parkinson's disease patients. It has 39 questions each with a response from 0-4 for a total of 156 points. The total score is calculated as a percentage so the scores of the 39 items are added and divided by 156 and multiplied by 100. The higher the score the worse quality of life.
A note on Outcomes	All collected data for pre-specified Primary and Secondary Outcome Measures should be reported. Data collected for exploratory outcomes can be included but is not required.	
Eligibility	Eligibility	Include protocol specific inclusion/exclusion criteria. Eligibility criteria should be entered in a bulleted list.
Contacts/Locations	Central Contact	Designate a member of the study team (Principal Investigator, Sub-investigator, Study coordinator) who potential participants can contact for more information. This person should be available via phone or email to field questions about the study. ● When a Central Contact is listed, a contact for each study location does not need to be listed. ● For KUMC Investigator-Initiated studies, it is recommended to provide a Central Contact and Location specific contacts
IPD Sharing Statement	Plan to Share IPD	Indicate whether individual deidentified participant data will be shared ("Undecided" does not satisfy ICMJE requirements). If yes, include information on what particular data will be shared, whether additional documents such as the protocol or statistical analysis plan will be available, when and for how long data will be available, and by what access criteria data will be shared.
References	Citations / Links / Available Study Data and Documents	Include any and all citations/links relevant to the study in this section. If you include this information in any other section (i.e. detailed description), Clinicaltrials.gov will require you to move it before approving the registration.

References

PRS User's Guide: https://prsinfo.clinicaltrials.gov/prs-users-guide.html#intro

PRS Registration Data Element Definitions: https://prsinfo.clinicaltrials.gov/definitions.html

PRS Training Materials: https://clinicaltrials.gov/ct2/manage-recs/present

PRS FAQs: https://clinicaltrials.gov/ct2/manage-recs/faq

Journal Article A Zarin, Deborah A.A Tse, Tony A Williams, Rebecca J. A Carr, Sarah "Trial Reporting in ClinicalTrials.gov — The Final Rule 2016" New England Journal of Medicine 2016; 375:1998-2004; November 17, 2016, 10.1056/NEJMsr1611785 http://www.nejm.org/doi/full/10.1056/NEJMsr1611785

ICMJE Policy: http://www.icmje.org/about-icmje/faqs/clinical-trials-registration/

NIH Policy: https://grants.nih.gov/policy/clinical-trials/reporting/understanding/nih-policy.htm

NIH Grantee Roles and Responsibilities: https://grants.nih.gov/clinicaltrials_fdaaa/faq.htm#B

Title 42 Part 11: https://www.ecfr.gov/cgi-bin/text-idx?SID=e617ec4da22678f934787ed565bbaa5a&mc=true&node=pt42.1.11&rgn=div