

Compliance Notice

Research Administration and Compliance

No. 17-003

May 16, 2017

NOTICE: OVERVIEW OF CLINICAL TRIALS REGISTRATION AND RESULTS REPORTING

This Compliance Notice relays an overview of the clinical trials registration and results reporting requirements as set forth by the Food and Drug Administration's (FDA) final rule that clarifies and expands upon Title VIII of the FDA Amendments Act of 2007 (FDAAA), the complementary National Institutes of Health (NIH) policy on the Dissemination of NIH-Funded Clinical Trial Information, and the International Committee of Medical Journal Editors' (ICMJE) clinical trial registration policy. Both the final rule and the complementary NIH policy were made publicly available on September 16, 2016, and became effective January 18, 2017.

Research teams are required to comply with the clinical trials registration and results reporting requirements as set forth by the FDA, NIH, and ICMJE. Virginia Commonwealth University (VCU) requires the registration of all clinical trials that meet ICMJE's definition of clinical trial.

If you plan to publish in an ICMJE member journal:

Read [ICMJE's Clinical Trial Registration policy](#).

The ICMJE requires "registration of clinical trials in a public trials registry [such as ClinicalTrials.gov] at or before the time of first patient enrollment as a condition of consideration for publication." More specifically, according to the ICMJE, "best practice dictates registration by the time of first patient consent." This requirement has been in effect since July 1, 2005.

"The ICMJE encourages posting of clinical trial results in clinical trial registries but does not require it. The ICMJE will not consider as prior publication the posting of trial results in any registry that meets [the ICMJE's] criteria if results are limited to a brief (500 word) structured abstract or tables (to include patients enrolled, key outcomes, and adverse events)."

ICMJE journals may not accept a manuscript if the author has failed to prospectively register his/her clinical trial. Note that exceptions to ICMJE's clinical trial registration policy are rare.

Furthermore, failure to publish may result in additional negative consequences including, but not limited to: negatively affecting an investigator's ability to obtain or retain funding, jeopardizing student support provided by the research, or compromising VCU's ability to meet the terms and conditions of the funding entity's award or contract.

Be aware that this registration requirement applies regardless of the funding source for the clinical trial.

If you plan to apply for NIH funds to support part or all of your clinical trial:

- 1) Read [NIH's September 15, 2016 Summary of HHS/NIH Initiatives to Enhance Availability of Clinical Trial Information](#).

This document provides an overview of the final rule and the complementary NIH policy and sets forth the legal requirements for compliance and the legal consequences of noncompliance. Most notably, this document includes definitions for essential terminology and timeframes for registration and results reporting.

- 2) Applications for NIH funding must include a plan addressing how ClinicalTrials.gov registration and results reporting requirements will be met. The Clinical Trials Registration Taskforce suggests the following language:

Dissemination of study results through ClinicalTrials.gov registration and reporting at a minimum will include the following components:

- *X (insert name or role, can be a designee) will be responsible for handling ClinicalTrials.gov requirements for this project under the PI's oversight. S/he will register the trial prior to enrolling the first subject. Once a record is established, s/he will confirm accuracy of record content; resolve problems; and maintain records including content update and modifications. S/he will also be responsible for aggregate results reporting and AE reporting at the conclusion of the project.*
- *Add specifics related to this trial.*

If the application for NIH funding is to support an Applicable Clinical Trial (ACT), the following language should also be included:

I certify that this submission contains an Applicable Clinical Trial (ACT) and I will ensure compliance with registration and results reporting submissions to ClinicalTrials.gov as required under the FDA Amendments Act of 2007 (FDAAA) and the Final Rule (42 CFR Part 11).

- 3) Consult with your school research administrators or center regarding the specifics for properly preparing and submitting an application to NIH.
- 4) NIH awardees must comply with the plan just as they would the other terms and conditions of the award.
- 5) NIH awardees must certify compliance with clinical trial registration and results reporting requirements in their progress reports and their competing renewal applications. NIH will verify that required information has been submitted before releasing any remaining funds for a grant or new funds for a future grant.

If you plan to conduct an investigator-initiated clinical trial involving an FDA-regulated drug, biological, or device product:

- 1) Read [NIH's September 15, 2016 Summary of HHS/NIH Initiatives to Enhance Availability of Clinical Trial Information](#).

This document provides an overview of the final rule and the complementary NIH policy and sets forth the legal requirements for compliance and the legal consequences of noncompliance. Most

notably, this document includes definitions for essential terminology and timeframes for registration and results reporting.

- 2) Use of the [Checklist for Evaluating Whether a Clinical Trial or Study is an Applicable Clinical Trial \(ACT\) is strongly encouraged to ensure early identification of ACTs](#). Note that ACTs have additional and different requirements, such as the required submission of Form FDA 3674 and the inclusion of specific language in informed consent forms.
- 3) For VCU faculty-held IND or IDE studies, consult go.vcu.edu/indide or email indide@vcuhealth.org regarding the specifics for properly setting up an investigator-initiated clinical trial involving an FDA-regulated drug, biological, or device product.
- 4) Certification of Compliance with ClinicalTrials.gov requirements must be included in the FDA application. See [Guidance regarding Certifications and Form FDA 3674](#).

Before Submitting to the Institutional Review Board (IRB):

- 1) Be aware that the final rule and complementary NIH policy require that a copy of the approved protocol, approved amendments, and statistical analysis plan (if not included in the protocol) be uploaded to ClinicalTrials.gov. All protocols that apply to all clinical trial Facility Locations must be uploaded as well. (42 CFR 11.48(a)(5))
- 2) Informed consent forms must include word-for-word the statement below relating to the posting of clinical trial information.

For ACTs: "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." (21 CFR 50.25(c))

For NIH-supported clinical trials that are not ACTs: "A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>. 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."

Roles and Responsibilities:

It is the responsibility of each group listed below to establish the necessary procedures to ensure they are in compliance with the final rule, the complementary NIH policy, and the ICMJE, as applicable. These procedures should be developed with the understanding that active communication and cooperation among the groups is essential to ensuring compliance with the various requirements.

Principal Investigators (PIs)

Although VCU as the Sponsor is the Responsible Party for all VCU investigator-initiated studies, the PI is ultimately responsible for determining whether his/her clinical trial needs to be registered. Once a PI determines that registration is required for his/her clinical trials, he/she must ensure that all registration and, if applicable, results reporting requirements are met. A PI who both initiates and conducts the study is known as the sponsor-investigator.

The PI is responsible for ensuring that IRB oversight is maintained until study completion and results reporting requirements for Applicable Clinical Trials and NIH-funded clinical trials have been satisfied. Studies that have not yet begun recruiting may be registered prior to IRB approval; however, the study record must be updated with the approval information prior to enrollment of the first subject.

If a study is being conducted at multiple institutions, the lead PI initiating the trial is responsible for registering the trial and for results reporting. It is the responsibility of the lead PI to coordinate obtaining all the necessary data to register the trial and for results reporting. Only one study record should be created in ClinicalTrials.gov per clinical trial.

PIs coming to VCU or leaving VCU and who are planning on transferring their clinical trials with them must make the proper preparations to transfer their clinical trial data and their ClinicalTrials.gov study records. To ensure a smooth transfer, the PIs will need to work with both institutions' clinical research offices and sponsored program offices.

ClinicalTrials.gov Program Administrator

The responsibilities of the ClinicalTrials.gov Program Administrator include but are not limited to:

- Serves as VCU's ClinicalTrials.gov Protocol Registration and Results System (PRS) Administrator.
- Maintains VCU's organizational account in ClinicalTrials.gov.
- Creates and disables ClinicalTrials.gov accounts as needed.
- Enables and disables access to ClinicalTrials.gov study records as needed.
- Releases study records to the PRS team for its review and for posting on ClinicalTrials.gov.
- Ensures that PIs register, update, and complete results reporting in compliance with the final rule, the complementary NIH policy, and the ICMJE, as applicable.
- Provides training, education, and assistance to PIs and all other individuals involved with the conduct of clinical trials at VCU to which the final rule, the complementary NIH policy, and the ICMJE apply.

Clinical Trials Reporting Manager for Massey Cancer Center

The responsibilities of the Clinical Trials Reporting Manager include but are not limited to:

- Serves as oncology and Massey Cancer Center's ClinicalTrials.gov Administrator and serves as the Record Owner for these clinical trials.
- Provides ClinicalTrials.gov-related training, education, data entry, and assistance to PIs and all other individuals involved with the conduct of oncology-related clinical trials.
- Ensures that oncology-related clinical trials are registered, updated, and have results reported in compliance with the final rule, the complementary NIH policy, and the ICMJE, as applicable.

General Procedures:

Registration

- 1) VCU follows the ICMJE's requirement regarding the deadline for registering a clinical trial in ClinicalTrials.gov.

The ICMJE requires "registration of clinical trials in a public trials registry [such as ClinicalTrials.gov] at or before the time of first patient enrollment as a condition of consideration for publication." More specifically, according to the ICMJE, "best practice dictates registration by the time of first patient consent."

- 2) Read the documents referenced in this Compliance Notice and consult with the suggested contacts to determine which specific registration and results reporting requirements apply to your particular clinical trial. The final rule, the complementary NIH policy, the ICMJE requirements, or any combination of the three may apply to your particular clinical trial.
- 3) Use the [E-CT.gov Account Create Request Form](#) to request that a ClinicalTrials.gov account be created for you and any study team member who may need one.

The individuals working on the ClinicalTrials.gov registration and results reporting must be intimately familiar with the study. It is important to note that only the Record Owner receives communications from PRS, so whoever is selected to be the Record Owner of your study record must be actively involved with the study record.

The PI must be either the Record Owner or on the Access List for the ClinicalTrials.gov study record.

Once an account is created in ClinicalTrials.gov, the user should receive an email from register@clinicaltrials.gov titled "ClinicalTrials.gov PRS Account Created." This email will give the user his/her login and temporary password.

- 4) Consult with PRS and/or the ClinicalTrials.gov Program Administrator or the Clinical Trials Reporting Manager for Massey Cancer Center. They can walk you through the protocol registration process step-by-step. This will establish the foundation for your results reporting, if applicable. There should be only one study record for each clinical trial.
- 5) Consult with a biostatistician or someone familiar with ClinicalTrials.gov. Be aware that registration sets the foundation for results reporting, if applicable.
- 6) Once you have completed the ClinicalTrials.gov Protocol Registration, click the "Entry Complete" button. Clicking the "Entry Complete" button is confirmation that the information you have entered into your study record is accurate and complete. Clicking this button also signals to the ClinicalTrials.gov Program Administrator that you are ready for your study record to be released.
- 7) Once the study record is released, the PRS team will review the study record for quality control (QC) purposes and post the study record on ClinicalTrials.gov. According to ClinicalTrials.gov's "Final Rule Results Information Requirements" webinar:
 - a) Information will be posted even if the QC process has not concluded.

- b) However, the study record will not receive an NCT number until the QC process has concluded.
- c) The posted study record will contain information to make clear that the QC process has not yet concluded for that particular study record.

8) ClinicalTrials.gov study records must be updated annually or more frequently as needed.

Note that some items require update within 15 or 30 days of a change (e.g., Recruitment Status, Primary Completion Date within 30 days, etc.). (42 CFR 11.64) Any major changes to the protocol (e.g., study requirements, study design, etc.) must be incorporated into the ClinicalTrials.gov study record in a timely manner.

Whenever a study record is updated, the updates will need to be re-released to PRS.

Results Reporting

9) The Final Rule requires that summary results information be submitted to ClinicalTrials.gov for any applicable clinical trial that is required to be registered, regardless of whether the drug, biological, or device products under study have been approved, licensed, or cleared for marketing by the FDA. (42 CFR 11.42)

10) In general, results information must be submitted no later than one year after the primary completion date of the clinical trial. Primary completion date is the date that the final subject was examined or received an intervention for the purpose of collecting the data for the primary outcome measure.

11) Results information submission may be delayed for as long as two additional years if a certification to ClinicalTrials.gov is submitted that either: 1) a drug, biological, or device product studied in the clinical trial is not yet approved, licensed, or cleared for marketing by the FDA *and* is still under development by the manufacturer; or 2) that the manufacturer is the sponsor of the clinical trial and has sought or will seek approval, licensure, or clearance for a new use of a product studied in the trial within one year. The Final Rule also permits requests for extensions to the results information submission deadline for “good cause.” (42 CFR 11.44) The FDA does not define “good cause,” but the circumstances for approving a “good cause” delay are expected to be very limited.

12) When uploading a copy of the approved protocol, approved amendments, and statistical analysis plan (if not included in the protocol) to ClinicalTrials.gov, the following must be included:

- the Official Title (as defined in § 11.10(b)(2)),
- NCT number (as defined in § 11.10(a)) (if available), and
- date of the protocol and the statistical analysis plan on the cover page of each document.

Names, addresses, and other personally identifiable information, as well as any trade secret and/or confidential commercial information (as those terms are defined in the Freedom of Information Act ([5 U.S.C. 552](#)) and the Trade Secrets Act ([18 U.S.C. 1905](#))) contained in the protocol or statistical analysis plan may be redacted prior to submission, unless such information is otherwise required to be submitted under this part.

The protocol and statistical analysis plan must be submitted in a common electronic document format specified at <https://prsinfo.clinicaltrials.gov>. (42 CFR 11.48(a)(5))

Quality Control

- 13) All apparent errors, deficiencies, and/or inconsistencies identified in the electronic notification from PRS must be addressed or corrected:
 - a) Within 15 calendar days for clinical trial registration information, or
 - b) Within 25 calendar days for clinical trial results information. (42 CFR 11.64(b)(1))

- 14) During the quality control process, PRS may identify various issues and flag the study record with various “problems.” To see and address the issue(s), the Record Owner or other designated user must:
 - a) Login to the [ClinicalTrials.gov Protocol Registration and Results System \(PRS\)](#).
 - b) Open the record.
 - c) From the Record Summary page, see the Next Step box and carefully review any Error and Warning messages and PRS Review Comments. These various messages are all indications that the record has problems of varying severity.
 - d) Edit the record as needed to address all Error and Warning messages and PRS Review Comments.

- 15) Other Corrections –Errors (other than those identified in the quality control process), must be corrected or addressed:
 - a) Within 15 calendar days for clinical trial registration information, or
 - b) Within 25 calendar days for clinical trial results information. (42 CFR 11.64(b)(2))

Response Plan for Problem Records:

Continued unresponsiveness or any other failure to adhere to the requirements and responsibilities set forth in this research compliance notice will result in an escalation of the matter to the Senior Associate Vice President for Research Administration and Compliance.

If VCU receives an FDA Notice of Noncompliance, the PI and Record Owner associated with the problem record will be notified that he/she must address the violations listed in the FDA Notice of Noncompliance immediately. If, after 15 calendar days, the PI is unresponsive or otherwise refuses to cooperate, VCU will transfer the Responsible Party designation for that particular study record to the PI. As the Responsible Party, the PI will be subject to any penalties for noncompliance.

Penalties for Noncompliance:

- 1) The FDA may impose civil monetary penalties for violations – an initial penalty up to \$11,383, and an additional \$11,383 per day until the noncompliance is resolved. Please note that this figure is as of January 2017 and likely will increase in the future. (42 CFR 11.66)

- 2) A responsible party who commits a prohibited act(s) as defined by the FDA may be the subject of an injunction action or criminal prosecution brought by the Department of Justice.

Examples of prohibited acts include: 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; and submission of clinical trial information which is false or misleading in any particular. (42 CFR 11.66)

- 3) Failure to comply with the terms and conditions of an NIH funding award may lead to grants enforcement actions, including termination of funding. (42 CFR 11.66)
- 4) Journals that abide by ICMJE guidelines will not publish manuscripts from authors who have failed to prospectively register their clinical trials.

Contact:

For Massey administered clinical trials:

Angela T. Rosas
Clinical Trials Reporting Manager
Massey CC Administrative Services
(804) 628-1896
atrosas@vcu.edu

For all other clinical trials:

Alanda R. Perry Jones
ClinicalTrials.gov Program Administrator
Wright Center for Clinical and Translational Research
(804) 628-9395
cctrctgov@vcu.edu

Forms:

- 1) [Checklist for Evaluating Whether a Clinical Trial or Study is an Applicable Clinical Trial \(ACT\)](#)
- 2) [ClinicalTrials.gov Protocol Registration and Results System \(PRS\)](#)
- 3) [E-CT.gov Account Create Request Form](#)
- 4) [Guidance regarding Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402\(j\) of The Public Health Service Act, Added By Title VIII of The Food and Drug Administration Amendments Act of 2007 \(Form FDA 3674\)](#)
- 5) [Questions and Answers on Informed Consent Elements, 21 CFR § 50.25\(c\)](#)

Source Documents:

- 1) [Federal Register: Clinical Trials Registration and Results Information Submission \(Final Rule\)](#)

- 2) [ICMJE Clinical Trial Registration policy](#)
- 3) [NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information](#)
- 4) [Regulations Implementing FDAAA 801](#)
- 5) [Section 801 of the Food and Drug Administration Amendments Act of 2007 \(FDAAA\)](#)

Related Documents:

- 1) [Final Rule Webinar Series](#)
- 2) [ICMJE Clinical Trials Registration FAQs](#)
- 3) [JAMA Article: “Toward a New Era of Trust and Transparency in Clinical Trials”](#)
- 4) [NEJM Article: “Trial Reporting in ClinicalTrials.gov – The Final Rule”](#)
- 5) [Summary of HHS/NIH Initiatives to Enhance Availability of Clinical Trial Information](#)
- 6) [Wright Center for Clinical and Translational Research ClinicalTrials.gov Program](#)

Issued by,

Signed copy is on file in the VCU OVPRI Research Administration and Compliance Office

Susan Robb, CRA	Date
Senior Associate Vice President	
for Research Administration and Compliance	