PM-307–Results Reporting of Clinical Trials in ClinicalTrials.gov

1. PURPOSE:

To describe the process for reporting results for a clinical trial already registered on ClinicalTrials.gov.

Please refer to SOP PM-306 – Registration of Clinical Trials in ClinicalTrials.gov regarding the creation of an account and registration of a clinical trial on ClinicalTrial.gov.

2. SCOPE:

This SOP will provide instruction and promote consistency among all departments within UTRGV regarding the requirement of registering applicable clinical trials with ClinicalTrials.gov. The US Food and Drug Administration (FDA) is the government agency that requires registration of clinical trials. Section 801 of the Food and Drug Administration Amendments Act of 2007 (FDAAA 801 or US Public Law 110-85) passed on September 27, 2007, requires mandatory registration and results reporting for certain clinical trials of drugs, biologics, and devices of all applicable clinical trials initiated on or before September 27, 2007, and is ongoing as of December 27, 2007. The legislation coupled with the Final Rule for Clinical Trials Registration and Results Information Submission (42 CFR Part 11) creates the regulatory requirements and procedures for ClinicalTrials.gov.

The International Committee of Medical Journal Editor (ICMJE) member journal requires, as a condition of consideration for publication in their journals, registration in a public trials registry. The ICMJE does not advocate one particular registry, but its member journals require authors to register their trial in a registry that meets several criteria.

According to the Food and Drug Administration Act of 2007:

- Penalties may include civil monetary penalties up to $10,000 fine for failing to submit or for submitting fraudulent information in ClinicalTrials.gov.
- After notification of non-compliance, the fine may go up to $10,000 per day until resolved.
- For federally funded grants, penalties may include withholding or recovery of grant funds.

2.1 REQUIREMENTS

Ultimately the results of all interventional studies need to be submitted in ClincalTrials.gov.

2.1.1 FDA Regulated Research Requirements:

- FDAAA requires registration and results reporting of ‘Applicable Trials’.

- Interventional studies;
- Studies involving drugs, biologics, or medical devices regulated by FDA;
- Studies that require an IND or IDE;
- Studies that have at least one site in the US or one of its territories or the product is manufactured in and exported from the US or one of its territories.
- Studies that are not Phase I (drug or biological products) or not Device Feasibility (device products)
- ClinicalTrials.gov within 21 days after the enrollment of the first patient.

For more information regarding 'Applicable Trials', see Elaboration of Definitions of Responsible Party and Applicable Clinical Trials (ACTs). ClinicalTrials.gov also provided the Checklist and Elaboration for Evaluating Whether a Clinical Trial or Study is an Applicable Clinical Trial (https://prsinfo.clinicaltrials.gov/CT_Checklist.pdf) as a reference.

2.1.2 ICMJE Requirements:

The ICMJE requires, and recommends that all medical journal editors require, registration of clinical trials in public trials registry at or before the time of first patient enrollment as a condition of consideration for publication. Editors requesting inclusion of their journal on the ICMJE website list of publications that follow ICMJE guidance should recognize that the listing implies enforcement by the journal of ICMJE's trial registration policy. http://icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html

2.1.3 Medicare Requirements:

Effective January 1, 2015, all Medicare qualifying trials, including some Phase I and device feasibility trials, are required to be registered into the ClinicalTrials.gov database. National Clinical Trial (NCT) numbers are required on clinical research related claims in order to receive payment. Patients should not be enrolled on a trial unless the NCT registration number is in place.

2.1.4 NIH Funding:

The National Institutes of Health (NIH) Policy on Dissemination of NIH-Funded Clinical Trial Information requires registration and results reporting, and applies to all clinical trials funded by NIH, regardless of whether they are subject to the FDAAA 801 and the Final Rule effective January 18, 2017. The Policy is effective for competing applications and contract proposals submitted on or after January 18, 2017, and states that all NIH funded awardees and investigators conducting clinical trials will register and report the results of their clinical trial in

ClinicalTrials.gov. Please refer to the following grants policy information from NIH's Office of Extramural Research to learn more about ensuring compliance with NIH's implementation of FDAAA 801:
https://grants.nih.gov/policy/clinical-trials/reporting/index.htm

Please refer to SOP PM-306 – Registration of Clinical Trials in ClinicalTrials.gov regarding the creation of an account and registration of a clinical trial on ClinicalTrial.gov.

3. REPONSIBLE INDIVIDUALS

3.1 FDA Regulated Research Requirements:

According to federal law, the 'Responsible Party' is responsible for reporting results to ClinicalTrials.gov and is defined as:

3.1.1 The IND/IDE holder of the trial

3.1.2 For studies not conducted under an IND/IDE

- The study sponsor or grantee institution
- PI if there is no external funding agreement

3.1.3 Situations in which Institution/PI is the Responsible Party

For trials being conducted under a funding agreement, grant (e.g., NIH awards) or department/internal funding, the funding recipient is considered the Responsible Party. The PI is in the best position to understand the research protocol study results and adverse events, therefore, the institution will designate the PI to assume the role of the Responsible Party.

- In situations where UTRGV serves as the primary site for a clinical trial and the institution is determined to be the "Responsible Party", the institution will designate this responsibility to the PI.

3.1.4 Situations in which the Institution/PI is NOT the Responsible Party

For most industry sponsored trials, the sponsor will be the Responsible Party, and, as such, the institution and PI will NOT have to manage submissions or results reporting to ClinicalTrials.gov. Similarly, for multi-center trials, or trials sponsored by other academic sites, only the lead site (Overall PI) typically bears responsibility for ClinicalTrials.gov reporting; site PIs typically do not have to do additional reporting.

3.1.5 What are the criteria for designating the PI as the "Responsible Party" for results reporting?

According to federal law, the PI can serve as a Responsible Party if that individual:

- Is responsible for conducting the trial.
- Has access to and control over the data from the clinical trial.
- Has the right to publish the results of the trial.

3.2 ICMJE Requirements

Anyone involved in the clinical trial could register the trial. In practice this responsibility usually falls with the individual submitting the publication to the ICMJE journal, which is usually the PI.

3.3 Medicare Requirements

In order to ensure proper research billing compliance, it is the responsibility of department research personnel to communicate the NCT number to their Research Finance Specialist (RFS) during administrative study start-up and prior to any patient enrollment on the trial. It is the responsibility of the RFS to associate the appropriate NCT number with study related claims and assure communication to the appropriate parties in revenue cycle management.

3.4 NIH Requirements

The trial's Responsible Party is responsible for two basic elements of compliance:

3.4.1 The registration of the ACTs in ClinicalTrials.gov

3.4.2 The reporting of summary results information (including adverse events)

3.4.3 All NIH grantees, regardless of whether or not they are the "Responsible Party" under FDAAA are responsible for:

- Certification that the responsible party has made all required submissions to ClinicalTrials.gov for ACTs funded in whole or in part by the NIH. This certification is done in the grant application and progress report forms.

4. RELATED TERMS AND DEFINITIONS

Applicable Clinical Trials (ACT)

National Clinical Trial (NCT) Number - another term for the ClinicalTrials.gov registry number unique to each record. The format for the ClinicalTrials.gov registry number is "NCT" followed by an 8-digit number (e.g., NCT00000419).

Protocol Registration and Results System (PRS)

Primary Completion Date (PCD)

Please reference the Standard Operating Procedures Glossary of Terms for complete definitions of terms in this SOP.

5. POLICY STATEMENT

All applicable clinical trials must have results reported in ClinicalTrials.gov. The Primary Completion Date (PCD) determines the time frame for results reporting.

The Responsible Party has one year (12 months) from the PCD to enter trial results. If a results submission is delayed, the Responsible Party must submit an extension request to ClinicalTrials.gov. Please see https://www.clinicaltrials.gov/ct2/manage-recs/fdaaa For information regarding delays and extension requests.

5.1 Updating Your Registered Study

Once a trial is registered, both the FDA and ICMJE require that registrations be updated as follows:

5.1.1 FDA updating requirements:

- Information must be updated at least once every 12 months.
- If changes affect human subjects via a protocol amendment, the information must be updated within 30 days of the IRB's approval.
- The registry must be updated within 30 days of any changes in recruitment status or completion of the study (PCD)*.
- Summary results (including adverse event information) need to be submitted not later than 1 year after the trial's primary completion date, with delays allowed in some circumstances.
- The registry must be updated within 15 days of change in approval or clearance status of drugs and devices not previously approved by FDA.

*Once a study is closed to accrual, the Responsible Party or designee will monitor the patient status (on treatment, off treatment, off study), to determine the PCD. This date can be entered into ClinicalTrials/gov as "anticipated" and updated as the study moves forward. Once the date is set as "actual" then the Responsible Party has one year from that date to enter results.

ClinicalTrials.gov notifies the Responsible Party (or designee) account of which trials are due for updates.

ICMJE requires updating study information every 6 months.

For the most up-to-date information or to cross reference the requirements for ClinicalTrials.gov please visit https://clinicaltrials.gov/ct2/manage-recs/faq

6. PROCEDURES

6.1 Results Reporting in ClinicalTrials.gov

Please be aware that because results are specific to each study, the procedures for results reporting are generic in order to be inclusive of all studies.

6.1.1 Helpful Tips:

- Be aware of fields marked with the following:
  - *Required by ClinicalTrials.gov
  - FDAAA – Required to comply with US Public Law 110-85, Section 801
- The system offers the option to save data if you do not have time to complete the entire process.
- Verify that all outcome measures in the ClinicalTrials.gov registration are correct before beginning the results reporting. These outcomes will automatically be copied to the results section.

6.1.2 Results Modules: there are nine modules of data to be completed.

- Participant Flow: Recruitment details, pre-assignment details, arm/group information, type of units assigned, and periods.
- Baseline characteristics: Arm/group information, baseline analysis population information, and baseline measure information.
- Outcome Measures: Outcome measure information, statistical analysis, statistical analysis overview, comparison group selection, type of statistical test, statistical test of hypothesis, method of estimation, and other statistical analysis.
- Adverse Event Information: The following tables must be completed: (1) All-Cause Mortality, (2) Serious Adverse Events, (3) Other (Not including Serious) Adverse Events. Additionally, time frame, adverse event reporting description, source vocabulary name for table default, collection approach for table default, arm/group information, adverse events, total number affected by all-cause mortality, total number at risk for all-cause mortality, total number affected by an serious adverse event, total number at risk for serious adverse events, frequency threshold for reporting (not including serious) adverse event above the frequency threshold, total number at risk for other (not including serious) adverse events, adverse event term, organ system, adverse event term additional description, source vocabulary name, collection approach, and adverse event data.
- Limits and Caveats: Overall limitations and caveats.
- Certain Agreements: Are all PIs employees of sponsor, results disclosure restriction on PIs, and PI disclosure restriction type.
- Results Point of Contact: Name or official title, organization name, phone, extension, and email.

- Delayed Results (Optional): Delay results type, intervention name(s), FDA application number(s), requested submission date, and explanation.
- Document Upload Information: Document type (study protocol, statistical analysis plan (SAP), informed consent form (ICF), or study protocol with SAP or ICF, document date, subtitle, and document.

6.1.3 Submitting Results

- The Protocol Registration and Results System (PRS) team at ClinicalTrials.gov will review the submission and post comments for corrections/clarifications. Depending on the nature of corrections, these can be done by the Responsible Party or designee as necessary. Once the review process is complete, ClinicalTrials.gov will send notification to the Responsible Party or designee that the submission of study results has been approved and will be published on the public ClinicalTrials.gov website within two business days.
- Secondary outcome results, if not reported at initial results submission, are reported when the data have been analyzed. Results must be reported within one year after the final patient has been given treatment unless an extension has been approved by the ClinicalTrials.gov PRS. Anticipated posting dates must be included at the time of the primary outcome results registry.
- If corrections or clarifications are requested by the ClinicalTrials.gov team, the Responsible Party [See Section 3 "Responsible Individuals"] must respond within 15 days for any registration related information and within 25 days for any results information.
- Once the results of the study are released by the Responsible Party, it will be reviewed by personnel at ClinicalTrials.gov within 30 days. Any comments are posted on the Responsible Party's account at ClinicalTrials.gov and an email will be sent to the Responsible Party. Corrections to trial results can be made, as needed, and the trial can be re-released. If there are no review comments the results are released to the public website within 2 business days following completion of the review period.

7. REFERENCES

- NIH Guidance on Clinical Trials Registration in ClinicalTrials.gov – https://grants.nih.gov/clinicaltrials_fdaaa/
- ClinicalTrials.gov public website – https://clinicaltrials.gov

- ClinicalTrials.gov registration site – https://register.clinicaltrials.gov
- Registration at ClinicalTrials.gov: Fact Sheet – http://prsinfo.clinicaltrials.gov/
- Definitions of a Responsible Party and Applicable Clinical Trial – https://prsinfo.clinicaltrials.gov/ElaborationsOnDefinitions.pdf
- Protocol Data Elements Definitions – https://prsinfo.clinicaltrials.gov/definitions.html
- ClinicalTrials.gov Training Materials – http://clinicaltrials.gov/ct2/manage-recs/present
- Learning Module 1: Clinical Trials.gov Overview and PL 110-85 Requirements – http://prsinfo.clinicaltrials.gov/WebinarSlidesBasicResults.pdf
- Frequently Asked Questions – https://clinicaltrials.gov/ct2/manage-recs/faq
- UTRGV SOP PM-306 Registration of Clinical Trials in ClinicalTrials.gov
- 42 CFR 11 https://www.govinfo.gov/content/pkg/CFR-2019-title42-vol1/xml/CFR-2019-title42-vol1-part11.xml
- PRS User Guide – https://prsinfo.clinicaltrials.gov/prs-users-guide.html

8. FORMS OR ATTACHMENTS

None