ClinicalTrials.gov: Registration and Enforcement

University of Maryland – Session VI

October 26, 2023

Presented by: Anthony Keyes, MBA, PMP, *Director, Johns Hopkins Clinical Trials.gov Program*
Kim Hill, Clinical Research Compliance Specialist

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Tips and Tricks for Entering Data

Kim Hill, Clinical Research Compliance Specialist

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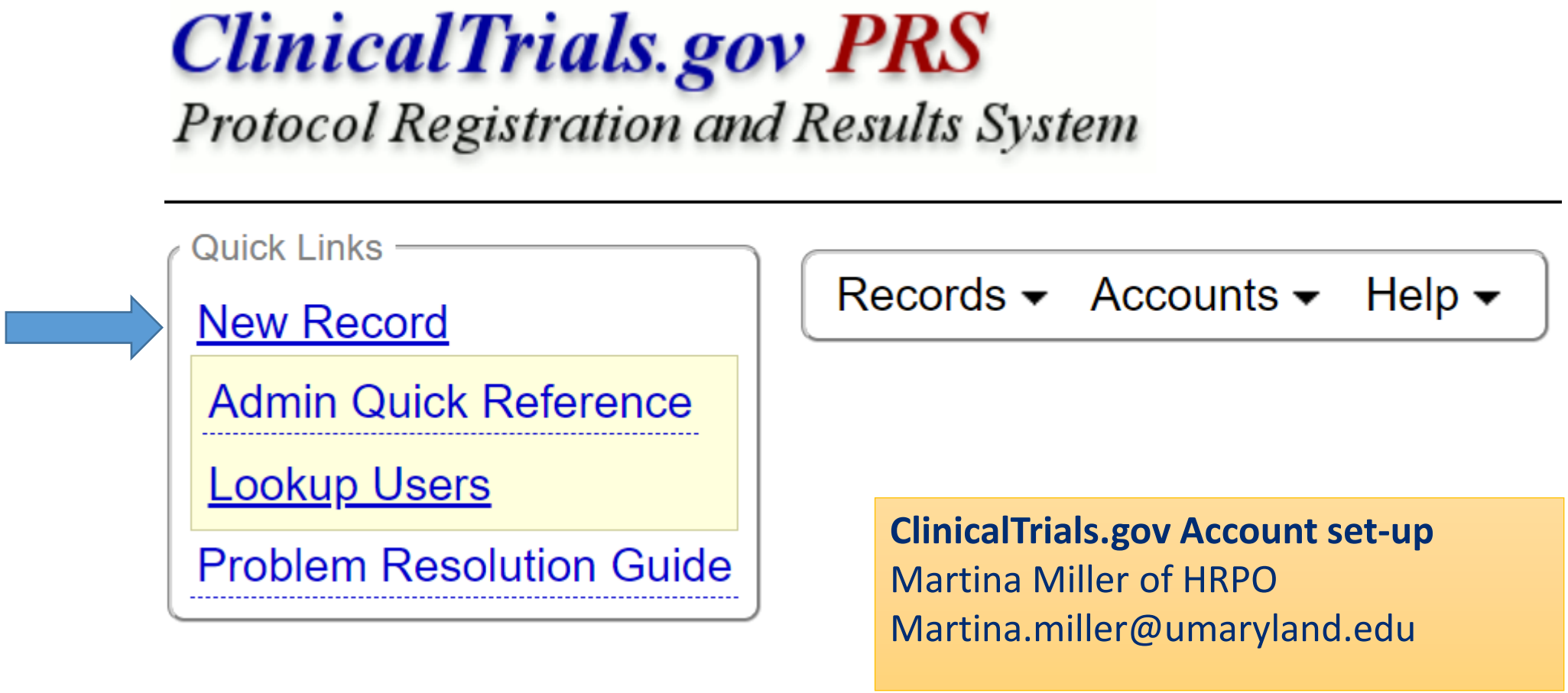
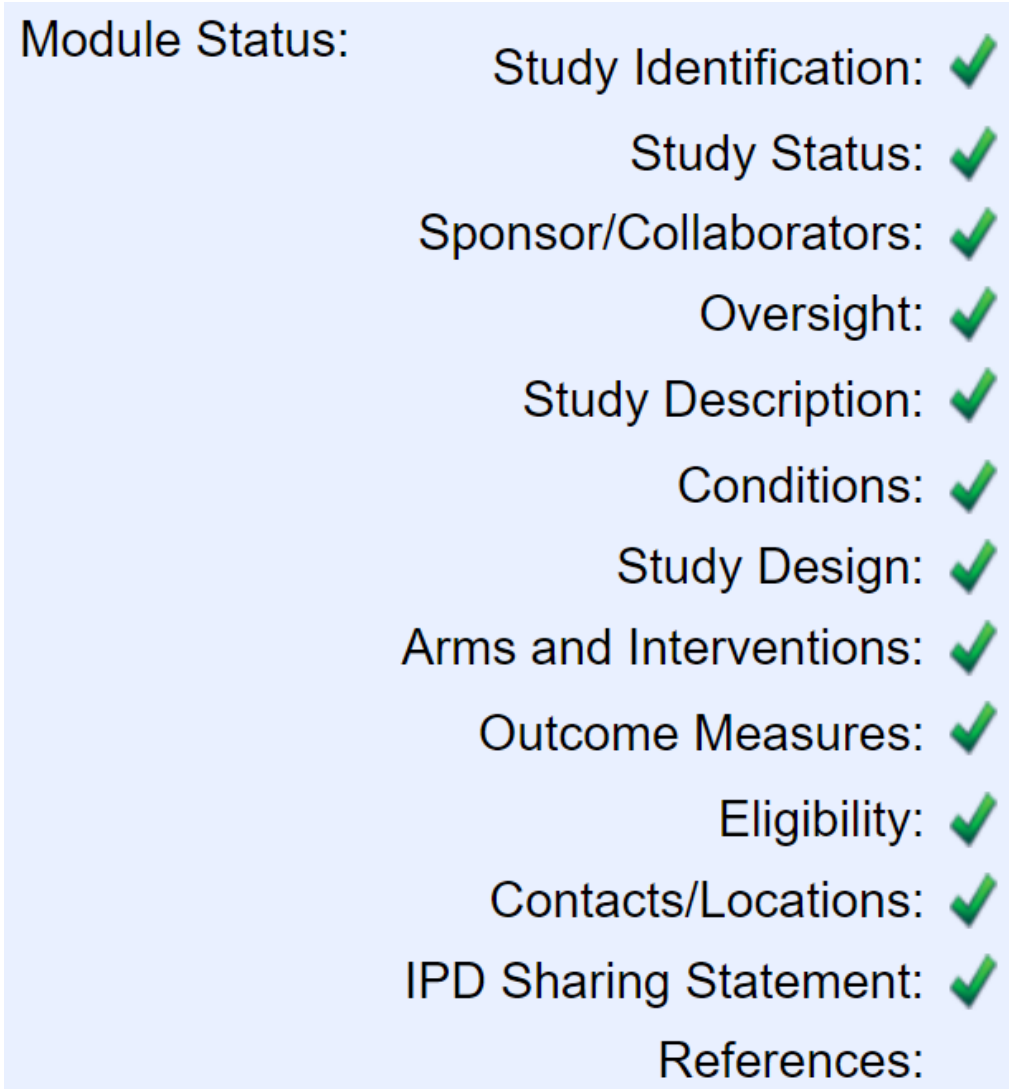
Registering the Record



ClinicalTrials.gov Account set-up
Martina Miller of HRPO
Martina.miller@umaryland.edu

Johns Hopkins
Institute for Clinical & Translational Research

Registering the Record



The System will guide you through each step

Help Definitions Spelling

Step-by-step videos

1. Registration
2. Results Reporting

- YouTube at "Johns HopkinsCTgov"

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Registering the Record at UMB

Study Identification

- **Unique Protocol ID**: IRB number (HP-000XXXXX)
- **Brief title** should be a short-form of the study title in language intended for the lay public
- **Acronym**: if entered it will be seen at the end of the Brief Title when the public sees it. Not a required field.
- **Official Title** should match the title in the IRB
- **Secondary ID:** could be used to enter the NIH grant number or other identifier. Not a required field.

Note: Any errors must be addressed so you can submit the record. Warnings should addressed to see if you need to make clarifications.

Registering the Record

Study Status

This section must be updated at least once a year or within 30 days of any changes

- **Record Verification Date:** the date you're entering the record or the date you're verifying all the information is up to date and correct.
- **Overall Recruitment Status:** use the dropdown list to choose the option that best applies to the current status of the study. *Recruiting*, *Not yet Recruiting*, etc. (can use Definitions for guidance)

Please note:

"Terminated" *studies are when participants were enrolled, but the study was closed prematurely;*

"Withdrawn" *studies are when no participants were enrolled.; use*

"Suspended" *if recruitment was stopped but may resume later.*

You'll need to provide a reason for these statuses.

Registering the Record

Study Status

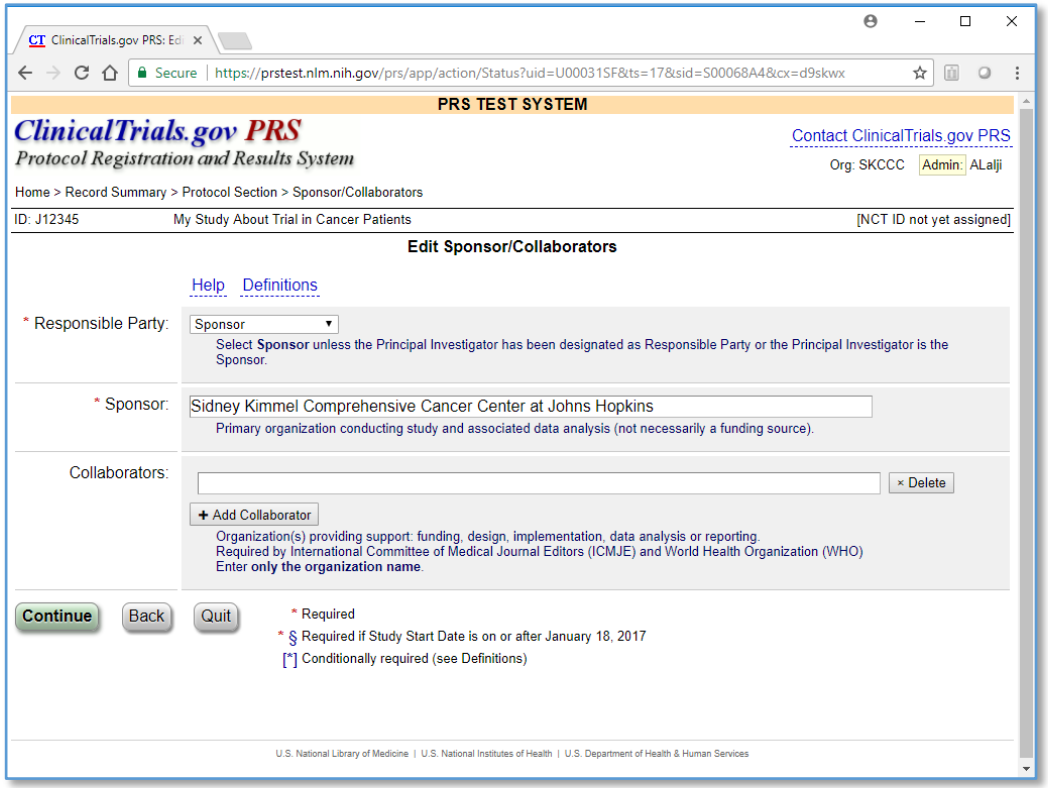
This section must be updated at least once a year or within 30 days of any changes

- **Study Start Date:** Enter your anticipated/actual start date (month and year)
- **Primary Completion Date:** use drop down to select Anticipated/Actual (month and year)
  Date when final data collection for the primary outcome measure will be collected – NOT data analysis.
- **Study Completion Date:** use drop down to select Anticipated/Actual (month and year)
  Date when final data collection for all other outcome measures will be collected – NOT data analysis.

Registering the Record

Sponsor/Collaborators

- **Responsible Party:** PI (Sponsor, Principal Investigator Sponsor-Investigator)
- **Sponsor:** is generally the primary organization or individual who initiated the study, not necessarily the funding source.
- **Collaborators:** all sources of support identified in IRB Support Information section



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Registering the Record

Oversight

The oversight section includes information about:

- *If you're studying a FDA regulated drug or biological product*
- *If your studying a FDA regulated device*
- *Human subjects protection (review board status, IRB contact information, and IRB study number)*

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Registering the Record

Study Description

- **Brief Summary** states the study's hypothesis or purpose; should be written in complete sentences and in language intended for the general public
- **Detailed Description (optional):** a detailed description of the study that doesn't replicate information found in other sections of the record. You can use the protocol you submitted to the IRB to complete this section. Don't include footnotes, citations, references, or eligibility criteria.

Tips and Tricks for Registering the Record

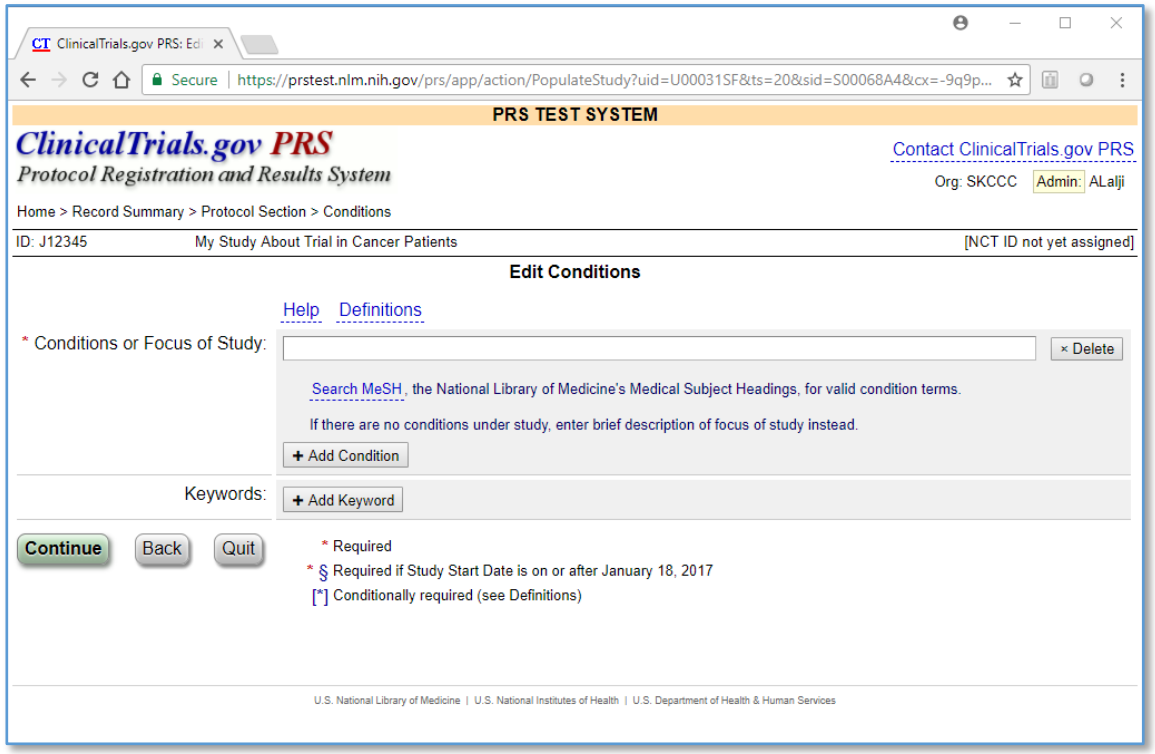
Formatting:

- Reviewers **don't accept personal pronouns** "*I, we, my, our, us*" becomes "the investigator(s)" or "the study team"; *"you, your, they, them, their"* becomes "the participant(s)"
- Remove all **parenthetical citations** (can use reference section which is an optional section)
- Use the **spelling feature** to check for spelling errors and unexpanded acronyms. All acronyms should be expanded on their first use
- Proof read for grammatical errors.

Registering the Record

Conditions and Keywords

- **Conditions or Focus of Study:** enter name of the disease or condition(s) being studied. As you start typing, the system will suggest conditions you can select.
- **Keywords:** enter associated words or phrases someone might use to search for the study. Key words should be listed one per line.



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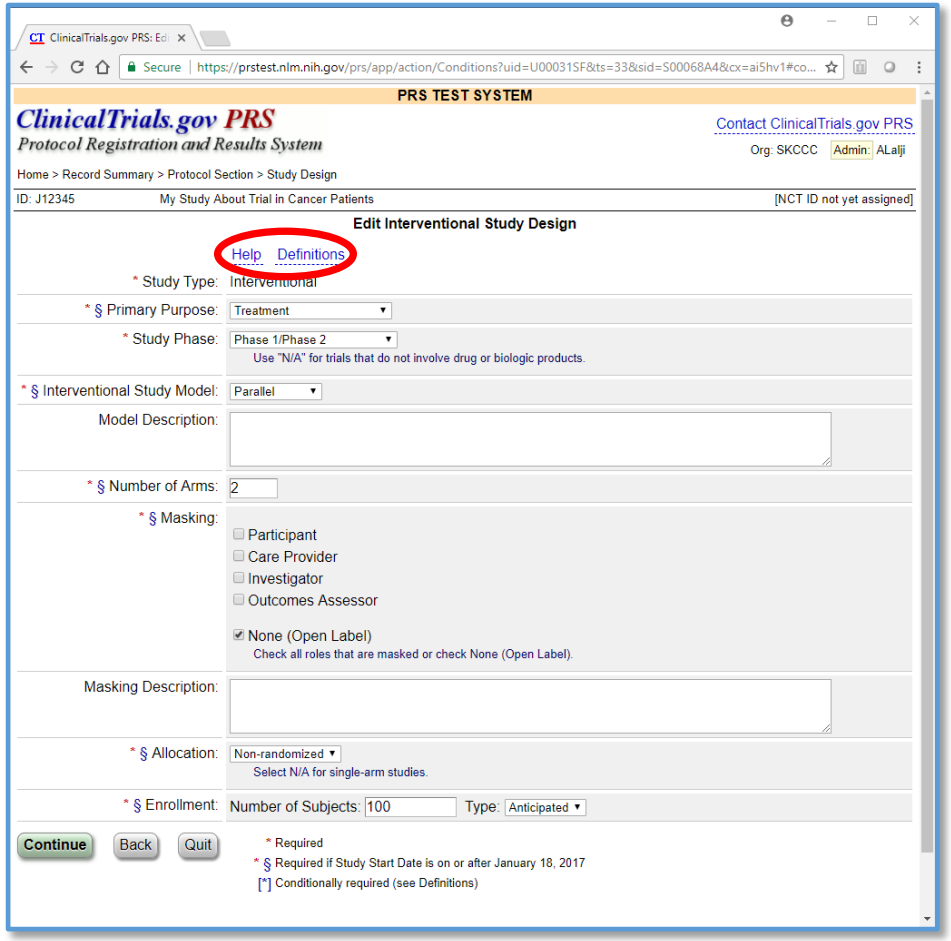
Registering the Record

Study Design

- **Study Type:** this is automatically populated
- **Primary Purpose:** select the option from dropdown
- **Study Phase: select option from dropdown** (if this study does not involve any drug or biologic products, select “N/A”
- **Interventional Study Model:** select the model that applies to this study
- **Number of Arms:** enter the total number of arms/groups for this study
- **Masking:** select who (if any) is being masked in this study
- **Allocation:** select randomization or “N/A” if only a single-arm study
- **Enrollment**: Enter the number of participants anticipated to be consented. Upon completion of the study, change the enrollment type to actual and update the number if necessary)



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Registering the Record

Arms

- **Arm Title:** enter a brief descriptive title that will distinguish it from other arms. (not Arm 1, and Arm 2)
- **Arm Type:** select the option that applies to each arm (experimental, placebo, no intervention, etc.)
- **Arm Description:** enter a description of the arm(s) such as dosage, method of administration, frequency and duration of the intervention.

Registering the Record

Interventions

- **Intervention Type:** select the intervention type from the dropdown menu (drug, device, behavioral, etc.)
- **Intervention Name:** enter the intervention name using the generic name or assigned drug label name for drugs and devices.
- **Other Intervention Names:** list alternative names for the interventions (i.e.,: brand name for drugs that people might search for)
- **Intervention Description:** provide a description of the intervention to be administered. You do not need to repeat what has already been stated within the Arms Description.

Each intervention must be listed separately.

Registering the Record

Arms/Intervention Cross-Reference

The information you provide about the arms and interventions will populate a grid.
Use the checkboxes to match the arm with the appropriate intervention.

Arms	Interventions		
	Drug: Durvalumab	Drug: Tremelimumab 300 mg	Drug: Tremelimumab 75 mg
Experimental: Cohort A - Durvalumab and Single-dose Tremelimumab	☑	☑	☐
Experimental: Cohort B - Durvalumab and Weekly-dose Tremelimumab	☑	☐	☑

Check boxes for Interventions associated with each Arm in the study.

Effective Outcome Measures

Entering Outcome Titles

Title: A brief, specific, descriptive title that describes **WHAT** is being measured

INCORRECT:

- Safety
- Adverse Events
- Area Under the Curve
- Blood Pressure
- Stress

CORRECT:

- Safety as assessed by number of participants experiencing serious adverse events
- Number of participants with treatment-related adverse events as assessed by CTCAE v5.0
- Area Under the Plasma Concentration Versus Time Curve (AUC) of [DRUG NAME]
- Change from Baseline in the Mean Seated Trough Cuff Systolic Blood Pressure at 6 Months
- Stress as assessed by the Everyday Stressors index

Effective Outcome Measures

Entering Outcome Descriptions

Description: A detailed description of **HOW** this outcome measure will be obtained or assessed. You must make sure to include applicable units of measure. If you're using a scoring scale, you must include the unabbreviated scale title, possible score range, and whether higher scores mean a better or worse outcome.

INCORRECT – "incidence of serious adverse events"
CORRECT – "Number of participants who experience adverse events ≥ Grade 3, as defined by Common Terminology Criteria for Adverse Events (CTCAE) v5.0"

INCORRECT: Pain score

CORRECT: The Short Pain Scale-11 is a validated self-reported instrument assessing average pain intensity over the past 24 hour period. Possible scores range from 0 (no pain) to 10 (worst possible pain).

Effective Outcome Measures

Entering Outcome Time Frames

Time Frame:

- Indicate the specific time point when the measurement will be assessed (e.g., 1 week);
- or the duration of time of assessment of the participant (e.g., from admission to discharge, up to 1 week);
- or a change between 2 time points (e.g., baseline and 8 weeks).

INCORRECT – “at time of intervention,” “at start of study,” “Days 1, 28, 60, 90”
CORRECT – “Day 1,” “Day 1 post-intervention,” “Change from baseline to Day 28”

Note: Each specific time point must be entered separately if you’re not assessing a change between time points or assessing pharmacokinetics..

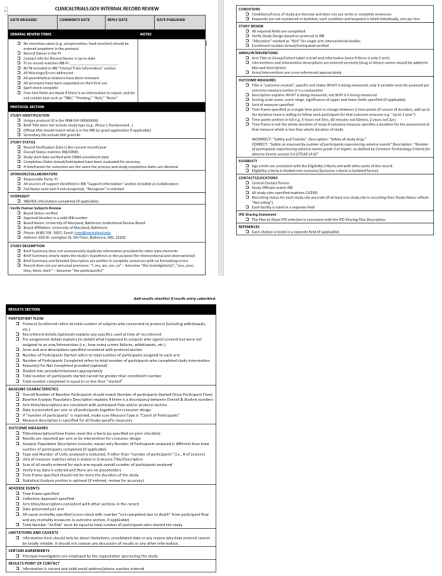
Using the Checklist

CLINICALTRIALS.GOV INTERNAL RECORD REVIEW

DATE RELEASED	COMMENTS DATE	REPLY DATE	DATE PUBLISHED

GENERAL REVIEW ITEMS	NOTES
❑ No monetary value (e.g. compensation, food voucher) should be entered anywhere in the protocol ❑ Record Owner is the PI ❑ Contact info for Record Owner is up-to-date ❑ PI on record matches IRB PI: _____ ❑ NCT# included in IRB "Clinical Trials Information" section ❑ All Warnings/Errors addressed ❑ All parenthetical citations have been removed ❑ All acronyms have been expanded on their first use ❑ Spell-check complete ❑ Free-text fields are blank if there is no information to report, and do not contain text such as "TBD," "Pending," "N/A," "None"	

PROTOCOL SECTION



Spelling

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FDA and NIH Enforcement

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FDAAA 801 Violations

- Applies to Applicable Clinical Trials (ACT)
- Notices are is sent to the Responsible Party
  - —**Pre-Notice Letters** are **not** identified as an FDAAA 801 Violation and **not** identified in ClinicalTrials.gov
  - —**Notice of Noncompliance** Letters are identified as an FDAAA 801 Violation in ClinicalTrials.gov

https://prsinfo.clinicaltrials.gov/ACT_Checklist.pdf

FDA Enforcement

- FDA has sent 53 **Pre-Notice Letters**
- **FDA has sent 4 Notice of Noncompliance** Letters

Responsible Party/Submitter	NCT Number	Notice of Noncompliance	Response Letter (if any)	Civil Money Penalty Amount (if any)
Ocugen	NCT03785340	4/15/2022	08/01/2022	
Petrikovets, Andrey M.D.	NCT03052816	8/31/2021	12/20/2021	
Accuitis Inc.	NCT03064438	7/26/2021	05/26/2022	
Acceleron Pharma, Inc.	NCT01727336	4/27/2021	12/13/2021	

- FDA has, **so far**, not issues any civil monetary penalties

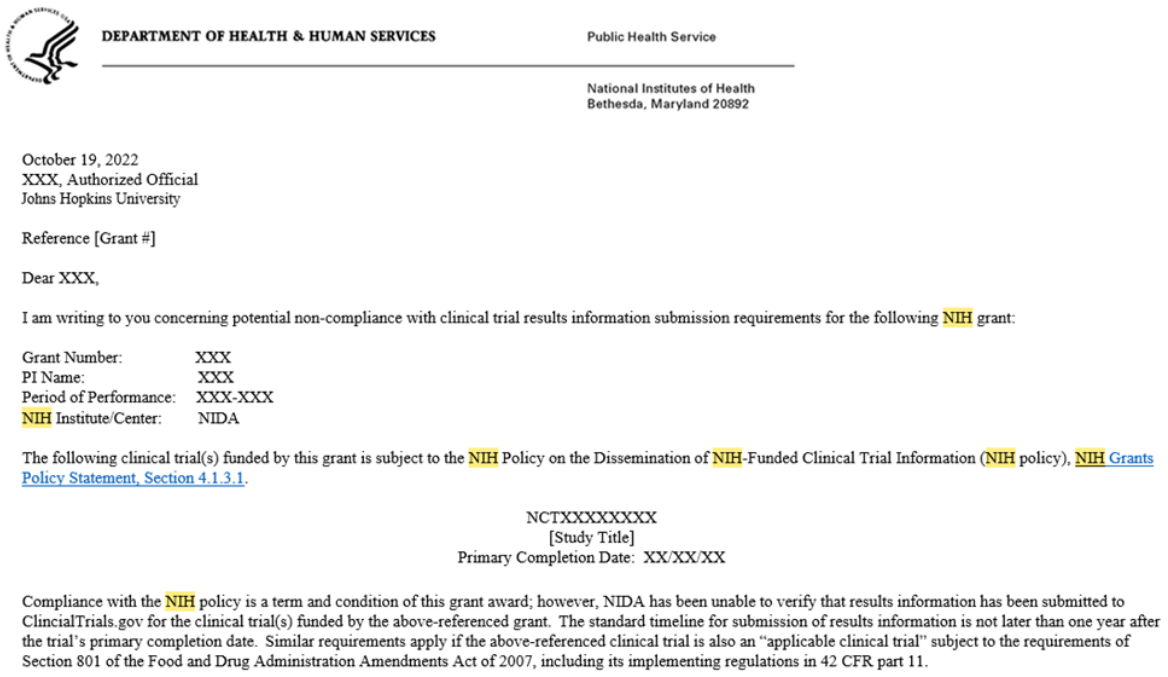
https://www.fda.gov/science-research/fdas-role-clinicaltrialsgov-information/clinicaltrialsgov-notices-noncompliance-and-civil-money-penalty-actions#:~:text=FDA%20has%20the%20authority%20to,or%20misleading%20clinical%20trial%20information

FDA/NIH Enforcement

- August 2022 Office of Inspector General (OIG) Report

  "NIH did not ensure that all NIH-funded Intramural and Extramural clinical trials complied with Federal reporting requirements"

- FDA and NIH are working together to identify and target noncompliance
- NIH has sent >300 Noncompliance Letters



DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

October 19, 2022
XXX, Authorized Official
Johns Hopkins University

Reference [Grant #]

Dear XXX,

I am writing to you concerning potential non-compliance with clinical trial results information submission requirements for the following NIH grant:

Grant Number: XXX
PI Name: XXX
Period of Performance: XXX-XXX
NIH Institute/Center: NIDA

The following clinical trial(s) funded by this grant is subject to the NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information (NIH policy), NIH Grants Policy Statement, Section 4.1.3.1.

NCTXXXXXXXX
[Study Title]
Primary Completion Date: XX/XX/XX

Compliance with the NIH policy is a term and condition of this grant award; however, NIDA has been unable to verify that results information has been submitted to ClincialTrials.gov for the clinical trial(s) funded by the above-referenced grant. The standard timeline for submission of results information is not later than one year after the trial's primary completion date. Similar requirements apply if the above-referenced clinical trial is also an "applicable clinical trial" subject to the requirements of Section 801 of the Food and Drug Administration Amendments Act of 2007, including its implementing regulations in 42 CFR part 11.

https://oig.hhs.gov/oas/reports/region6/62107000.asp

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New NIH SOP

I. Purpose: To describe the recommended process for identifying NIH-funded clinical trials

II. Scope: This Standard Operating Procedure (SOP) applies to any Protocol Registration and Results System (PRS) Administrator within the Johns Hopkins enterprise.

New NIH SOP

All NIH-funded clinical trials regardless of study phase, type of intervention, or whether they are subject to FDAAA will be expected to register and submit results information to ClinicalTrials.gov per the NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information (NIH Policy)

- The Protocol Registration and Results System (PRS) contains an algorithm to assist in determining if a trial is an ACT or probable (pACT).
- There is presently no PRS algorithm to assist in determining if a trial meets the NIH Policy

New NIH SOP

When Johns Hopkins ClinicalTrials.gov Program staff (CTP) review a record, they should use the checklist which includes opening the record in the Institutional Review Board (IRB) and verifying that monetary funding source information reported in Section 9 – Support Information is entered into the PRS

- —Records with NIH-funding recorded in the PRS as “Secondary IDs” or with the name of the NIH institution recorded under “Collaborators” will be displayed in the PRS Planning Report under the “NIH Grants” column.
- —CTP uses the “NIH Grants” column in the PRS Planning Report to identify records that are NIH-funded (ACTs or non-ACTs) with a Primary/Study Completion Date in the current month and sends an e-mail to the Principal Investigator/Record Owner to verify the dates are correct
    - If the date is correct CTP sends a results entry reminder approximately 8 months later (4 months before results are due) with continual reminders until results are entered
    - If the date is incorrect the date is updated with an actual date of completion or a future, anticipated date

New NIH SOP

Approximately monthly a member of the Office of Research Administration (ORA) workflow team should send CTP a spreadsheet with federal awards funded that month that have the Clinical Trial Indicator in Section IV of the Notice of Grant Award = “Yes”.

CTP should cross-reference the ORA spreadsheet with data in the PRS.

- CTP may open the record in PRS and in the IRB to ensure that the NIH institution recorded in the ORA spreadsheet is listed under “Collaborators” in the PRS
  - Should the NIH Institution not be listed in the IRB, the CTP should flag the record in the IRB for the NIH Institution to be added at the next change in research or continuing review
- CTP may open the record in PRS and in the IRB to ensure the grant number is recorded in the PRS as a “Secondary IDs”
  - Should the grant number not be listed in the IRB, the CTP should flag the record in the IRB for the grant number to be added at the next change in research or continuing review

New NIH SOP

Additional clarification may be found using NIH RePORTER to identify grants where the NIH Spending Category = “Clinical Research; Clinical Trials and Supportive Activities” and/or the Project Terms list “Clinical Research”

Types of Studies

- 1) Clinical Trials funded either in whole, or in part by the National Institutes of Health (NIH) with grant applications submitted on or after January 18, 2017

  Institutes of Health (NIH) Definition of a Clinical Trial: A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

https://www.hopkinsmedicine.org/institutional-review-board/guidelines-policies/organization-policies/103-25

Types of Studies

- 2) Qualifying clinical trials which will render claims for items and services to the Center for Medicare and Medicaid Services (**CMS**):

  The National Clinical Trial (NCT) number must be included on claims for items and services provided in clinical trials that are qualified for coverage as specified in the "Medicare National Coverage Determination (NCD) Manual," Section 310.1

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https://www.hopkinsmedicine.org/institutional-review-board/guidelines-policies/organization-policies/103-25

Types of Studies

- 3) Studies supported by a foundation who is a signatory to the May 18, 2017 WHO, International Clinical Trials Registry Platform (ICTRP):

  Many Non-governmental organizations (NGOs) and foundations such as the Bill and Melinda Gates Foundation, and the Wellcome Trust require registration and results reporting.

https://www.hopkinsmedicine.org/institutional-review-board/guidelines-policies/organization-policies/103-25

Types of Studies

- 4) "Applicable Clinical Trials" (ACTs) subject to registration and reporting requirements under the Food and Drug Administration's Amendments Act (FDAAA) which include the following:
  - —Trials of Drugs/Biologics: Controlled, clinical investigations of a product subject to FDA regulations. This includes preliminary studies or phase I trials to be published in an ICMJE journal.
  - —Trials of Devices: Controlled trials with health outcomes, other than small feasibility studies, and pediatric post-market surveillance.
  - —The trial has one or more sites in the U.S.
  - —The trial is conducted under an FDA Investigational New Drug Application (IND) or Investigational Device Exemption (IDE) application
  - —The trial involves a drug, biologic, or device that is manufactured in the U.S. or its territories and is exported for research

https://www.hopkinsmedicine.org/institutional-review-board/guidelines-policies/organization-policies/103-25

Questions?

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

See us on YouTube at "JohnsHopkinsCTgov"

Email us with any questions at
registerclinicaltrials@jhmi.edu

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