ClinicalTrials.gov
Common Challenges and Solutions

John C. Hicks
Clinical Research Services Office

Lara Fournier
Knight Cancer Institute
Learning Objectives

Upon session end, participants should be able to:

• Explain CTgov disclosure/reporting requirements
• Identify common issues and related solutions
• Know what to do with CTgov when a PI has indicated they are leaving OHSU
See a QR Code?

Scan an on-screen QR code with your phone’s camera to view content related to the slide.

QR codes are selectable hyperlinks in published versions of this slide deck.
What is ClinicalTrials.gov?

• Federal database of clinical trials: https://clinicaltrials.gov

• Maintained by National Library of Medicine (NLM)

• Studies registered and maintained through the Protocol Registration and Results Reporting System (PRS) via https://register.clinicaltrials.gov
Why Report to ClinicalTrials.gov?

• Ethical responsibility to the public

• Impacts worldwide clinical research effort, activities, and outcomes

• Required by U.S. law and policies
Who Registers?

**Responsible Party:**

- The sponsor of the study, OR...

  - The principal investigator (PI) if they:
    - Have access to and control over the data
    - Have rights to publish study results, **AND**
    - Are able to satisfy ClinicalTrials.gov submission req’s

  – Cancer-related studies, PI or study team can contact Knight Research Administration at [ctrp-admin@ohsu.edu](mailto:ctrp-admin@ohsu.edu) for assistance.
Which Studies Must Report?

- Policies influence responsibilities + deadlines;
  More than one requirement may apply

  - National Institutes of Health (NIH)

  - Food and Drug Administration Amendments Act (FDAAA)

  - International Committee of Medical Journal Editors (ICMJE)
NIH Policy

✓ Does the study receive direct NIH funding?
✓ Does the study have a start date on/after 18-JAN-2017?
✓ Is the study a “clinical trial” as defined by NIH?

An answer of YES to ALL of the above criteria indicates:
- ClinicalTrials.gov registration and record upkeep is required, AND
- Reporting results to ClinicalTrials.gov is required

An answer of NO to ANY of the above criteria indicates:
- The study does not fall in the scope of NIH policy
FDAAA Law

✓ Is the study type interventional?
✓ Does the study examine an FDA-regulated clinical investigation of a drug, biologic, or device?
✓ Is the study conducted at ≥1 USA site, OR, is it conducted under IND/IDE?
✓ Is the trial other than a phase 1 (drug/biologic) or device feasibility study?
  • Includes Early phase 1 (formerly known as Phase 0).

An answer of YES to ALL of the above criteria indicates:
- ClinicalTrials.gov registration and record upkeep is required, AND
- Reporting results to ClinicalTrials.gov is required

An answer of NO to ANY of the above criteria indicates:
- FDAAA law/regulation does not require this study to report
ICMJE Policy

✓ Is the study type interventional?
✓ Does the study examine the effect of a health-related intervention on a health-related outcome?

An answer of YES to the above criteria means:
- ClinicalTrials.gov registration and record upkeep is required, HOWEVER
- Reporting results to ClinicalTrials.gov is optional

An answer of NO to ANY of the above criteria indicates:
- Publishers do not require this study to report
## Summary of Responsibilities by Requirement

<table>
<thead>
<tr>
<th></th>
<th>NIH Policy</th>
<th>FDAAA Law</th>
<th>ICMJE Policy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SCOPE</strong></td>
<td>NIH-funded “clinical trials”, as defined by NIH; Please check with your program officer</td>
<td>Applicable Clinical Trials (ACT) as defined by FDAAA</td>
<td>Interventional clinical trials (broad scope of intervention)</td>
</tr>
<tr>
<td><strong>WHEN TO REGISTER</strong></td>
<td>Record registration visible on ClinicalTrials.gov no later than 21 days after first subject enrollment</td>
<td>Record registration visible on ClinicalTrials.gov no later than 21 days after first subject enrollment</td>
<td>Record registration visible on ClinicalTrials.gov prior to date of first subject enrollment</td>
</tr>
<tr>
<td><strong>RESULTS REPORTING</strong></td>
<td>Report results no later than 12 months after the Primary Completion Date</td>
<td>Report results no later than 12 months after the Primary Completion Date</td>
<td>No requirement for reporting results. Therefore, consider FDAAA for results reporting.</td>
</tr>
<tr>
<td><strong>PHASE OF TRIAL</strong></td>
<td>All phases</td>
<td>Excludes Phase 1 (drug) and Feasibility (device)</td>
<td>All phases</td>
</tr>
<tr>
<td><strong>TYPE OF TRIAL</strong></td>
<td>All (including behavioral, diagnostics, dietary supplements, etc.)</td>
<td>All FDA regulated drugs, biologics and devices</td>
<td>All (including behavioral, diagnostics, dietary supplements, etc.)</td>
</tr>
<tr>
<td><strong>IF FOUND NON-COMPLIANT</strong></td>
<td>- Principle Investigator loses funding</td>
<td>- Public notice</td>
<td>- Immediate rejection from ICMJE journals prior to peer review</td>
</tr>
<tr>
<td></td>
<td>- OHSU loses funding</td>
<td>- FDA sanctions</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Civil monetary penalties (up to $10,000+/record/day)*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Loss of HHS funding to study and/or OHSU</td>
<td></td>
</tr>
</tbody>
</table>
Additional Policy Consideration

• Revised Common Rule (2018)
  – Requires posting of template informed consent form within a specific time frame
Common Rule

✓ Is the study supported by a federal entity (NIH, DoD, etc.)?
✓ Must the study comply with 2018 Common Rule requirements?

An answer of YES to the above criteria means:
- The study must post one (1) IRB-approved informed consent form (ICF) to its CTgov registration or a docket folder on regulations.gov
- Consent form must have been used to enroll at least 1 study subject

An answer of NO to ANY of the above criteria indicates:
- Study does not need to upload an ICF
Common Rule (cont.)

When to post informed consent form:
✓ After recruitment closes
✓ No later than 60 days after last subject last visit

Find study’s 2018 Common Rule applicability via eIRB:
Common Challenges & Solutions
CHALLENGE:
Report to CTgov on Time

• Uncertainty if registration/results reporting required
• Registration/updates performed late or never at all
• Results submission performed late or never at all
• Underestimation of time/effort needed to complete reporting/disclosure processes
SOLUTION:
Use Guidance Resources

• Start early
• Getting started guide
• Determination flowchart
• Disclosure deadlines
• Strategy development
• Presentations and slide decks
• Cancer-related? Review materials above, then contact ctrip-admin@ohsu.edu
SOLUTION:

CTgov Disclosure Support Portal
CHALLENGE:

Complete the Reporting Process

• Registration or results were entered in the PRS but never Released
• Registration or results were Released but were returned with issued PRS Review Comments
• Addressing of PRS Review Comments never performed
SOLUTION:
Understand PRS Process Flow

Reminder, there are 4 activities in PRS: 1) In Progress, 2) Complete, 3) Approve, 4) Release – you have to click all 4 actions to fully release the record to publish to public CTgov.

START HERE

PRS data entry → Record Released → PRS analyst review

Review Comments issued → NOT ACCEPTED

ACCEPTED

Posted to ClinicalTrials.gov

NOT PUBLIC → PUBLIC
SOLUTION:

Follow Up to Ensure Completion

• Check the PRS routinely
• Read PRS Review Comments & make revisions as needed
• Follow up with the Principal Investigator
• Ask for help from CRSO, Knight Research Admin, or ClinicalTrials.gov
• When done, make sure to click ‘Release’ activity
CHALLENGE:
Specify Responsible Party

• Responsible Party is set incorrectly
• Confusion over who/what is the Responsible Party
• PI does not have technical authority in the PRS to Approve and Release a registration
**SOLUTION:**

**Revise the Responsible Party**

- In PRS → Protocol Section → Sponsor/Collaborators
- Refer to earlier “Who registers?” slide or CTgov definitions
- For most studies
  - Responsible Party = Principal Investigator
    - Enables the PI to complete the final ‘Release’ action
- Exceptions
  - IND/IDE? Responsible Party = IND/IDE Holder
  - Pediatric postmarket surveillance of a device product
**SOLUTION:**

Revise the Responsible Party

- **Responsible Party:** Principal Investigator
  - Select Sponsor unless the Principal Investigator has been designated as Responsible Party or the Principal Investigator is the Sponsor.

  **Investigator Information**
  - Investigator Name [Username]:
  - Investigator Official Title:
  - Investigator Affiliation: Oregon Health and Science University

- **Sponsor:** Oregon Health & Science University
  - Primary organization conducting study and associated data analysis (not necessarily a funding source).

- **Collaborators:**
  - + Add Collaborator
  - Organization(s) providing support: funding, design, implementation, data analysis or reporting. Required by International Committee of Medical Journal Editors (ICMJE) and World Health Organization (WHO)
  - Enter only the organization name.

 leaps

- **Required**
- **$ Required if Study Start Date is on or after January 18, 2017**
- [*] Conditionally required (see Definitions)
CHALLENGE:

List Collaborators

• Study is funded but Collaborators module is left blank
• Study receives other external support but Collaborators module is left blank
**SOLUTION:**

List All Supporting Organizations

- CTgov defines Collaborators as any organization providing support for the study, including funding
- List funders providing support and other supporting organizations
  - Include NIH, OHSU Foundation, OCTRI, other collaborating medical centers.
  - Studies with dedicated grants, list grant ID (e.g. ‘R01DA013131’) in the secondary IDs section
CHALLENGE:

PI is Leaving/Has Left OHSU

- CTgov registration records abandoned
- Reporting responsibilities unfulfilled
- PI difficult to contact after departure
**SOLUTION:**

Plan Ahead for PI Departure

- Check the PRS for departing PI study registrations
  - Look for: Active/ongoing studies
  - Look for: Finished studies pending results reporting
- Identify new Responsible Party for studies staying at OHSU
- Identify any studies that will need to move with PI to their new organization
**SOLUTION:**

**Seek Assistance**

- Refer to PI departure flowchart
- Ask for help
  - Noncancer studies may notify CRSO of PI departure
  - Cancer studies may reach out to Knight staff (ctrp-admin@ohsu.edu)
CHALLENGE:

ICMJE Data Elements in the PRS

• Data elements required by ICMJE left blank or missing

✓ Unique Protocol ID (IRB#)
✓ Secondary IDs
✓ Name of Sponsor + Collaborators
✓ Facility Contact or Central Contact Person
✓ Overall Study Official(s)
✓ Brief Title
✓ Official Title
✓ Facility Information–Country
✓ Primary Disease Condition or Focus of Study
✓ Intervention Type
✓ Intervention Name(s)
✓ Intervention Description

✓ Arm/Group Intervention Cross-Reference
✓ Arm Title
✓ Arm Type
✓ Arm Description
✓ Eligibility Criteria
✓ Sex/Gender
✓ Age Limits
✓ Accepts Healthy Volunteers
✓ Study Type
✓ Allocation
✓ Masking
✓ Interventional Study Model
✓ Primary Purpose
✓ Study Phase

✓ Study Start Date
✓ Enrollment (count)
✓ Overall Recruitment Status
✓ Primary Outcome Measure Information
✓ Secondary Outcome Measure Information
✓ Human Subjects Review
✓ Study Completion Date(s)
✓ IPD Sharing Statement
→ NEW AS OF 2019
✓ Results data elements (if required to report)
SOLUTION:

Use Guidance Resources

• Registration checklist
  – Labels modules that are required by ICMJE at the time of study registration
CHALLENGE:
Uploading Documents to the PRS

• Uncertainty which documents must be uploaded
• Uploading documents too early or late
• Specifying incorrect “Document Date”

Reminder: All documents uploaded to the Document Section of the PRS are posted to the study’s public ClinicalTrials.gov record
SOLUTION:

Know the Upload Requirements

• Protocol/statistical analysis plan (SAP)
  – Required for studies reporting results to CTgov
  – Upload ONLY at the time of entering results (within 12 months of actual primary completion date)
  – Upload in PDF/A format
SOLUTION:

Know the Upload Requirements

• Informed consent form (ICF)
  – Required ONLY for federally-funded studies that must comply with Revised Common Rule of 2018
  – Must be posted to the study’s public CTgov record within the specified time frame
SOLUTION:
Specify "Document Date"

• Use the date the document was last IRB-approved
• Make sure the Document Dates MATCH each other:
  ✓ Document Date entered in the PRS Document Section upon upload
  ✓ The date visible within the uploaded document
SOLUTION:
Add a Cover Page to Documents

• Specify these required data elements:
  – Document Date (date document was IRB approved)
  – NCT Number
  – Official Study Title
  – Investigator Name

• Consider using CRSO cover page template
SOLUTION:

Cover Page Template (PDF)

• Open in Adobe
• Edit fillable fields
• Save, then use Acrobat Pro to add as cover page to your document
CHALLENGE:
Outcomes are Not Well Defined

• Outcomes lack detail that describes what it getting measured
• Lumping multiple, different, outcomes into one
• Instruments and scales used are not defined
• Outcome timeframes are too vague
SOLUTION:
Write Detailed Outcomes

• Consider each outcome as a single measure that will hold a single discrete result value
  – Avoid ‘lumping’ (e.g. “Blood pressure and heart rate)
• Add enough detail so a lay reader can understand what is getting measured
• Describe scales (high/low value and what that means)
SOLUTION:
Write Detailed Outcomes

• Outcome timeframe needs to be specific to when it will be assessed. Example, “Study completion” is too vague.
  – Better: “Study completion, an average 1 year”
  – Better: “End of Cycle 1 (each cycle is 28 days)”

• Lastly, update your protocol so outcomes listed there are consistent with ClinicalTrials.gov
  – Remember your protocol is uploaded with results
CHALLENGE:
Underestimating Results Entry

• Studies that require results (FDAAA ACT, NIH Policy)
• Confusion around completion dates
• Submitting late
• Completion takes multiple rounds of review and QC feedback
SOLUTION:
Plan Ahead and Start Early

- Plan early for required results, ideally while protocol is getting drafted, keep the CTgov results requirements in mind
- Remember all primary and secondary outcomes will need to be reported as well baseline characteristics, participant flow and AE data.
- Leverage protocol templates that include required CTgov elements (outcomes/endpoints & timeframes)
SOLUTION:
Be Aware of Completion Dates

• Results due within 12 months of primary completion date (actual)
  – Plan to report all the outcomes as you have collected data on
• Primary completion date definition: when final data collected for primary outcome(s) and does not include analysis.
• Study completion date definition: when final data collected for all outcomes (primary, secondary, and adverse events)
  – Some secondary outcomes can be reported within 12 mos of study completion if timeframe specifies
SOLUTION:

Be Aware of the PRS Process

• Initial review of result submissions take 30 days
• Often they will come back with QC issues that need resolving (taking another 2-3 weeks for more PRS review)
• To avoid being late, get started soon after primary completion date
• Work with your statisticians (recommended)
CHALLENGE:

What if things change?

• Objectives change and/or
• One or more outcomes are no longer relevant and should be removed
• Issues obtaining data needed or enrollment
Solution:

Amend Protocol and Update CTgov

- Records can be updated as applicable to accommodate changes in research plan or objectives
- Promptly amend the protocol and update CTgov
- If feasible, update as soon it’s determined change is needed
- Avoid waiting to last minute (while submitting results) to remove outcomes
**SOLUTION:**

Update Status as Terminated

• In situations with poor enrollment and study ended early, set status in CTgov to ‘Terminated’ instead of ‘Complete’

• For outcomes where no data was obtained or not enough to analyze, can report ‘zero’ participants analyzed and supply an explanation