ClinicalTrials.gov

Common Challenges and Solutions

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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

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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

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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

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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

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Who Registers?

Responsible Party:

- The sponsor of the study, OR…

INESTIGATOR-INITIATED TRIALS

- 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 for assistance.*

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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)

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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 ClincalTrials.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

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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 ClincalTrials.gov is required

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

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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 ClincalTrials.gov is optional

An answer of NO to ANY of the above criteria indicates:
- Publishers do not require this study to report

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Summary of Responsibilities by Requirement

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

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Additional Policy Consideration

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

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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

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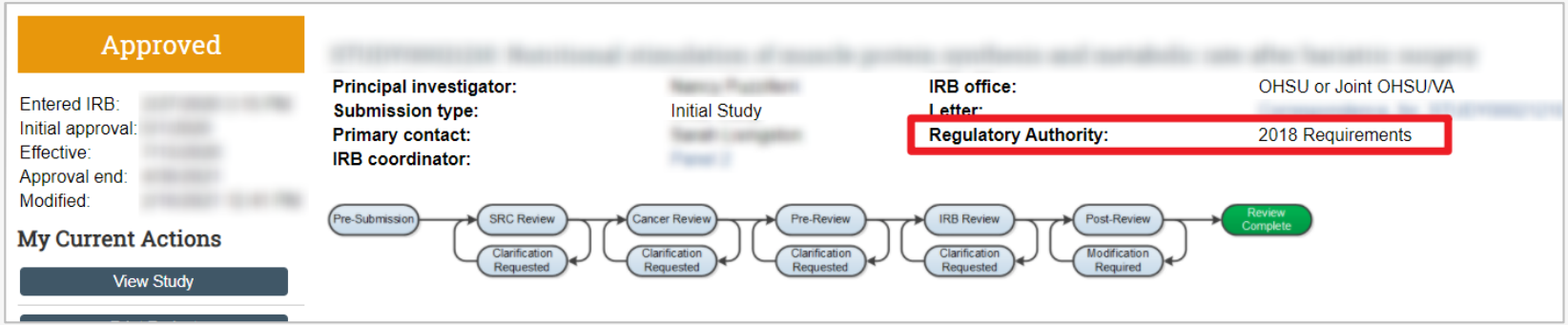
Common Rule (cont.)

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:



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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 ctrp-admin@ohsu.edu

CTgov Disclosure Support Portal

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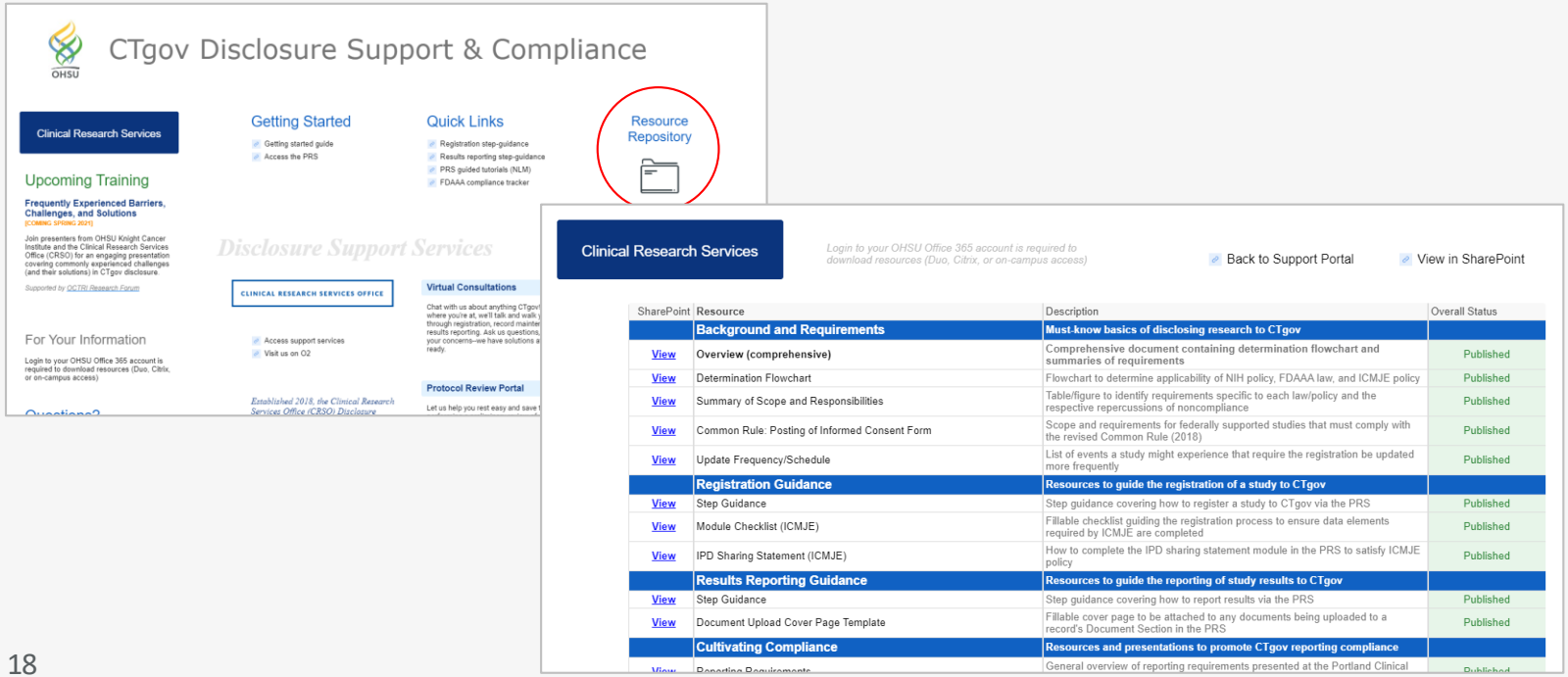
SOLUTION:

CTgov Disclosure Support Portal



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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

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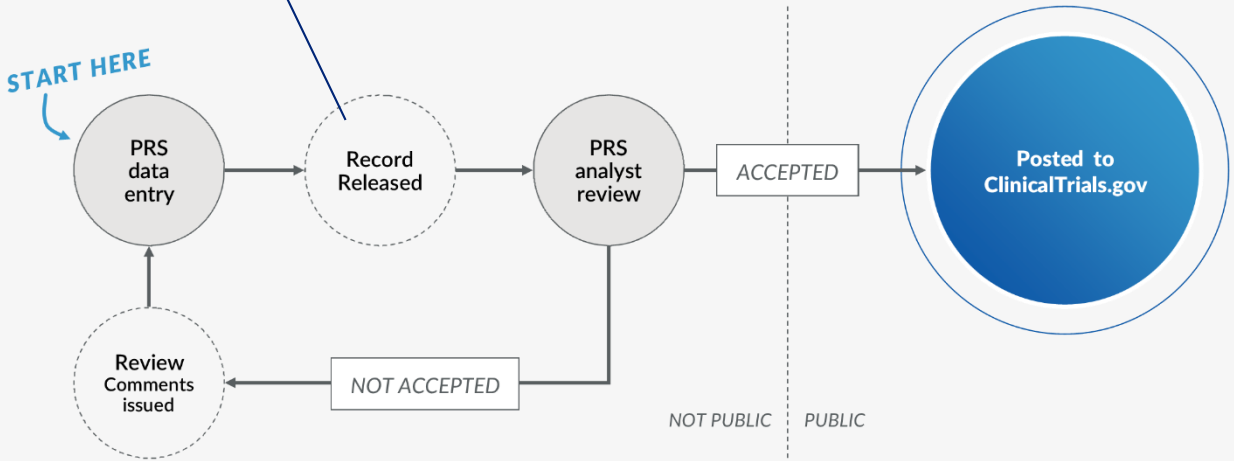
SOLUTION:

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.



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

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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

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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

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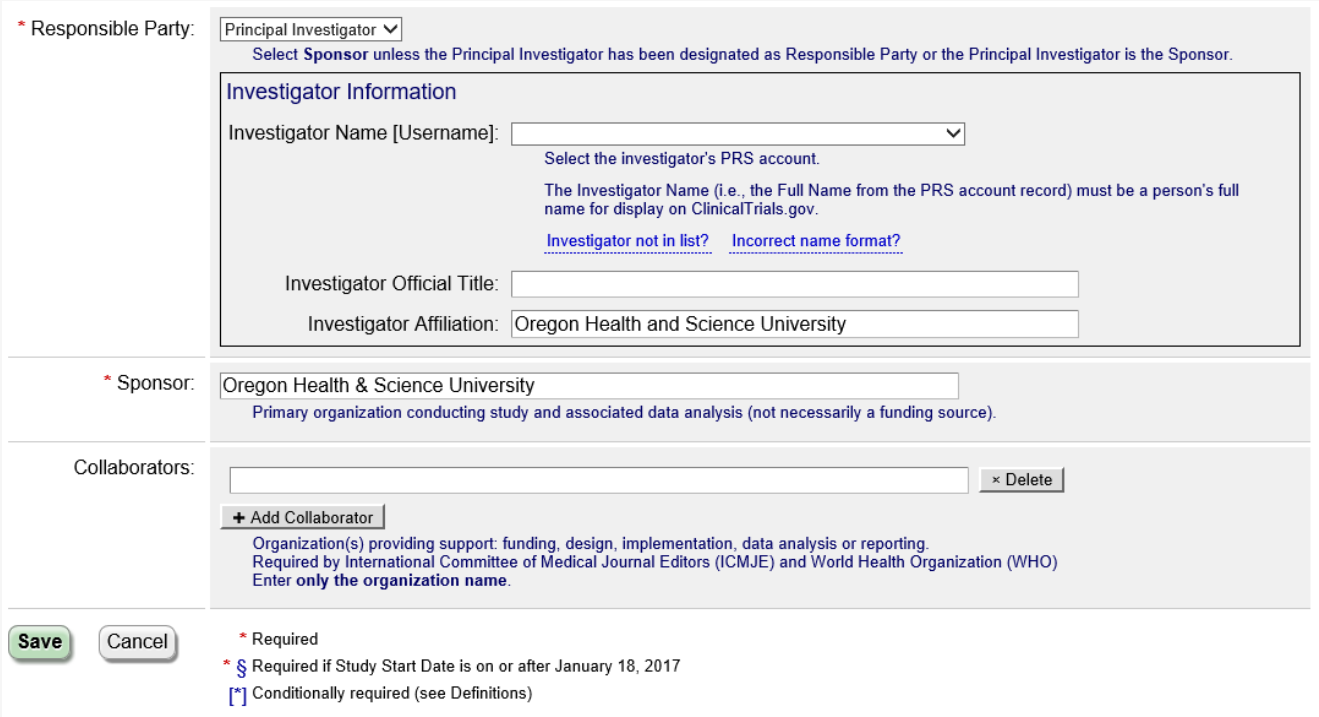
SOLUTION:

Revise the Responsible Party



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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

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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

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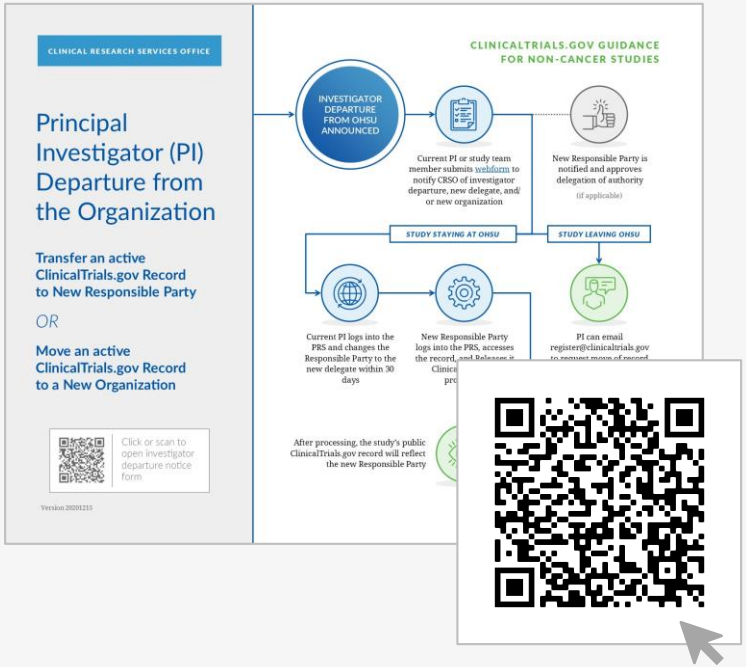
SOLUTION:

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)



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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)

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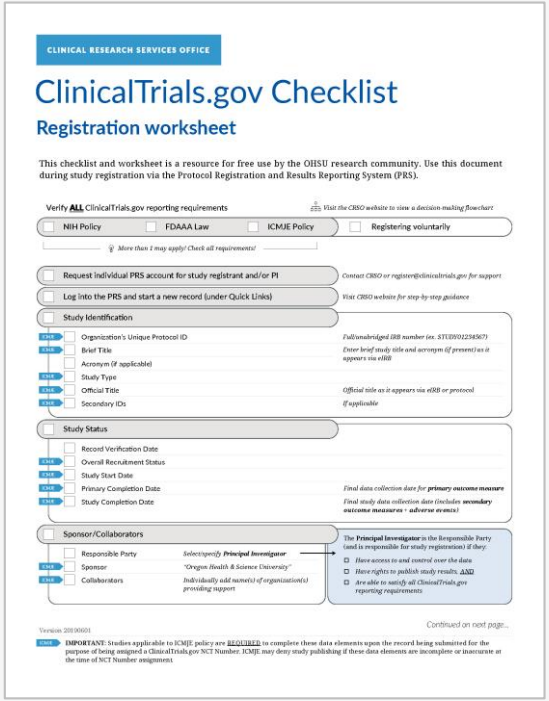
SOLUTION:

Use Guidance Resources

- Registration checklist
  - Labels modules that are required by ICMJE at the time of study registration



CLINICAL RESEARCH SERVICES OFFICE

ClinicalTrials.gov Checklist

Registration worksheet

This checklist and worksheet is a resource for free use by the OHSU research community. Use this document during study registration via the Protocol Registration and Results Reporting System (PRS).

Verify **ALL** ClinicalTrials.gov reporting requirements — *Visit the CRSO website to view a decision-making flowchart*

NIH Policy | FDAAA Law | ICMJE Policy | Registering voluntarily

More than 1 may apply! Check all requirements!

Request individual PRS account for study registrant and/or PI — *Contact CRSO or register@clinicaltrials.gov for support*

Log into the PRS and start a new record (under Quick Links) — *Visit CRSO website for step-by-step guidance*

Study Identification

- Organization's Unique Protocol ID — *Full/unabridged IRB number (ex. STUDY01234567)*
- Brief Title — *Enter brief study title and acronym (if present) as it appears via eIRB*
- Acronym (if applicable)
- Study Type
- Official Title — *Official title as it appears via eIRB or protocol*
- Secondary IDs — *If applicable*

Study Status

- Record Verification Date
- Overall Recruitment Status
- Study Start Date
- Primary Completion Date — *Final data collection date for **primary outcome measure***
- Study Completion Date — *Final study data collection date (includes **secondary outcome measures** + **adverse events**)*

Sponsor/Collaborators

- Responsible Party — *Select/specify **Principal Investigator***
- Sponsor — *"Oregon Health & Science University"*
- Collaborators — *Individually add name(s) of organization(s) providing support*

The **Principal Investigator** is the Responsible Party (and is responsible for study registration) if they:

- *Have access to and control over the data*
- *Have rights to publish study results, AND*
- *Are able to satisfy all ClinicalTrials.gov reporting requirements*

Continued on next page...

Version 20190601

IMPORTANT: Studies applicable to ICMJE policy are REQUIRED to complete these data elements upon the record being submitted for the purpose of being assigned a ClinicalTrials.gov NCT Number. ICMJE may deny study publishing if these data elements are incomplete or inaccurate at the time of NCT Number assignment

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*

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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 (with in 12 months of actual primary completion date)
  - Upload in PDF/A format

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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

Review Revised Common Rule

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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

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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

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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

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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)

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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

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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

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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)

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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

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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)

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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

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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

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CTgov Disclosure
Support Portal

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