Key Clinical Trial Requirements on ct.gov

Main Governing Bodies

- **FDA**
  - Applicable Clinical Trials
  - FDAAA 801 and Final Rule (effective 2007 and 2017)
- **NIH**
  - Dissemination of Information (effective 2017)
- **ICMJE**
  - International Committee of Medical Journal Editors
- **Others**
  - CMS: Center for Medicare and Medicaid Services,
  - Dept of Veterans Affairs

Summary of Requirements	Applicable Clinical Trials (ACTs): FDAAA 801 and 42CFR Part 11	NIH-Funded Clinical Trials: NIH Dissemination Policy	ICMJE Policy
Scope	Interventional Study of a FDA-Regulated drug, biological, and device products (not Ph1, SIND, feasibility)	Interventional studies, any Phase including behavioral studies, fully or partial funded by NIH	Any interventional Clinical Trials with health outcome
What & When			
Registration:	Register within 21 days of enrollment	Register within 21 days of enrollment	Register prior to enrollment
Annual Verification	every 12 months	every 12 months	every 12 months
Modifications:	within 15 - 30 days of change	within 15 - 30 days of change	within 15 - 30 days of change
Results:	One year of Primary completion date	One year of Primary completion date	Encouraged, but not required
Protocol (and statistical analysis plan if not in protocol):	One year of Primary completion date	One year of Primary completion date	Encouraged, but not required
ICF (Informed Consent Form):	Not required	After study is closed to recruitment, and no later than 60 days after the last study visit by any subject	Not required
Enforcement	Criminal proceedings and civil penalties (over $13,000/day); loss of HHS funding	Witholding/loss of NIH funding	Ineligibility to publish

Navigating New Mandates ClinicalTrials.gov An Investigators Perspective

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Understanding the Different Demands of the Investigator

Goals of a Grant

- Obtain funding to test hypothesis
- Provide human subject protocol in a concise manner
- Novel science is typically the driving force
- Intellectual ideas are potentially still fluid

Goals of clinicaltrials.gov

- Collect and share significant summary protocol information before and during the trial
- Summarize results and adverse events
- Provide transparency to patients, investigators, sponsors to build public trust.

How to Homogenize these Goals

- Collaborate with a clinical trialist EARLY
- If trial is multicenter, collaborate with a clinical trial organization or equivalent
- Interpret protocol as written in the grant into a clinical trial protocol for regulatory purposes, study implementation, and clinicaltrials.gov reporting.
- Simplify primary and secondary endpoints and use tertiary endpoints for exploratory outcomes

Current Disconnect

- In an effort to obtain grant funding, novel science is prioritized.
- To stay within budget limits, the human subject portion of the grant is woefully underfunded and tends to be an after thought.
- The full cost of human subject research is under estimated and not fully understood.
- Budgeted funds directed toward human subject study are disproportionately utilized by data management to meet mandates such as clincaltrials.gov, etc

Entering Study

- ClinicalTrials.gov is designed to cover ALL clinical studies, therefore, as a user, you will think “my study doesn’t fit”. You have to make it fit☺

http://www.ClinicalTrials.gov/beta/manage-recs/fdaa#WhenDoINeedToRegister-

- User pearls
  - Proper entering of a trial impacts downstream events
  - Enter your study in the most basic and simple form as possible
  - REALISTICALLY enter study start and study completion dates.
  - “Estimated” primary outcome completion endpoint (***date the last participant was examined or received intervention and data collected***) Of note….has NO relation to timing of data analysis.
  - Determination of intervention arms AND Arms/Groups are important because all results must be reported based upon this delineation
  - Responsible party identified as the sponsor or PI
  - Reporting requirements will change. When they change, they are retroactive to ALL active studies. Close studies in a timely manner.

Reporting Results

- Results and Adverse events must be reported within 12 months of the “actual” data of primary outcome completion endpoint, but you will receive queries based upon estimated date.
- Results must be reported within 30 days of FDA approval.
- Other reporting elements must be current, ie overall study status, actual completion date (in the past), enrollment
- User pearls
  - Overall study status must be consistent with study start/completion dates and can not be “recruiting” or “not yet recruiting”
  - Enrollment must be actual and the SAME as the number “started” in participant flow
  - Results section must be consistent with Intervention Names in protocol
  - Results section must be consistent with Arms/Groups in protocol

http://prsinfo.clinicaltrials.gov/results_definitions.html

Closing a Study

- Reporting requirements will change.
- When they change, they are retroactive to ALL active studies.
- Close studies in a timely manner.
- ???

Disseminating Results

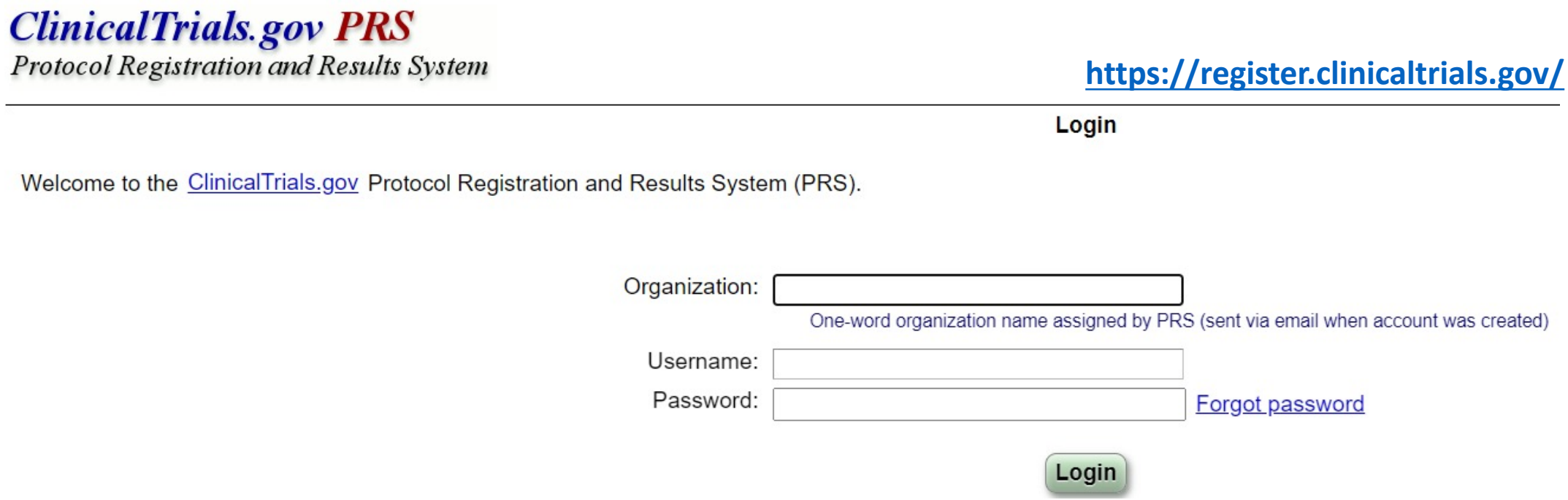
- Historically, the investigator was focused on
  - Final report to sponsor
  - Manuscript publication in a high impact journal
- Now, additionally focus on results in clinicaltrials.gov

It is the gift that keeps on giving

(or taking)☹

Registration, Maintenance, & Results Reporting in Clinicaltrials.gov

Registering a Study

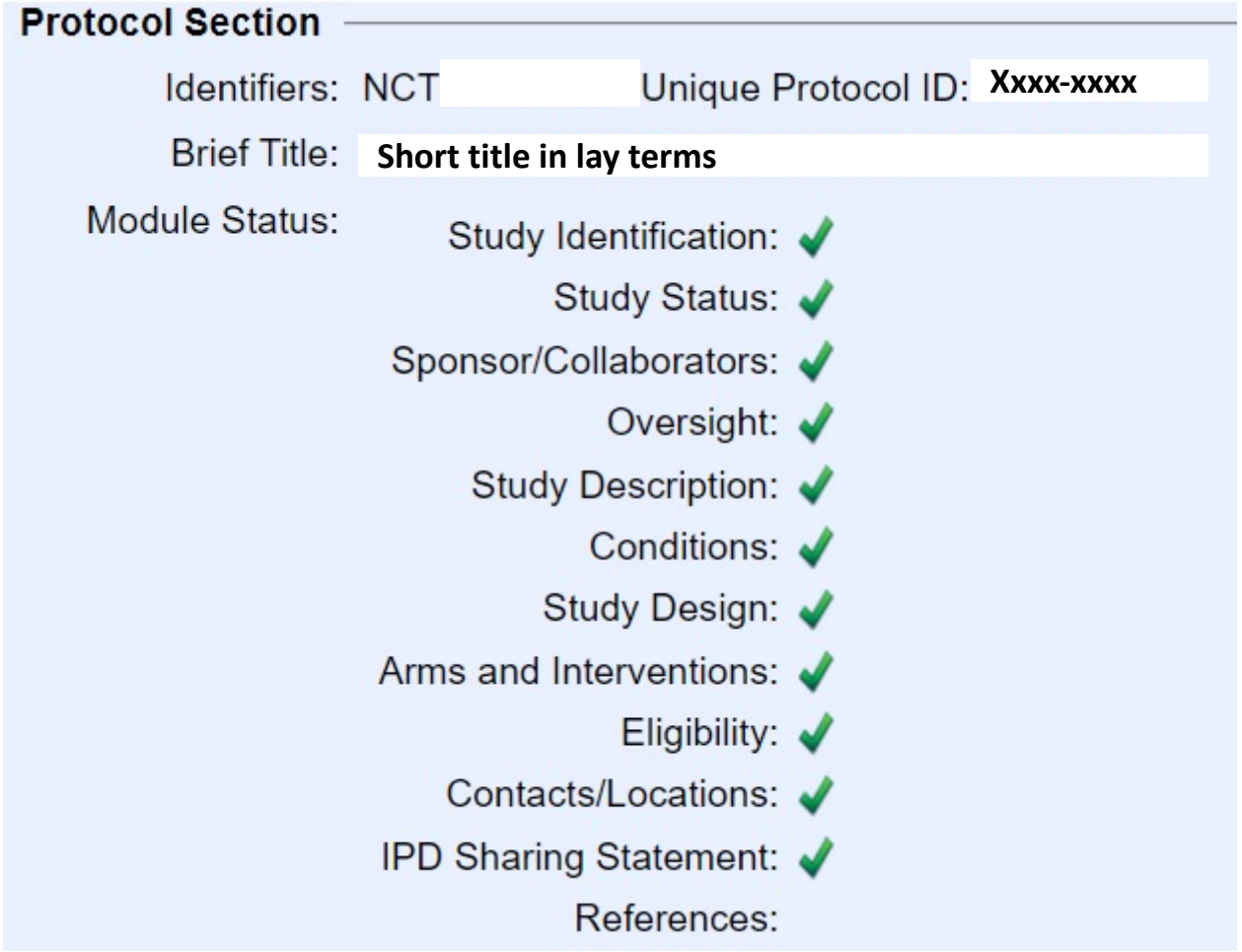


- Registration is required by law and for journal publication

The ICMJE emphasizes that such exceptions should be rare, and that authors failing to prospectively register a trial risk its inadmissibility to our journals.

Registering a Study

- Enter the required data elements: https://prsinfo.clinicaltrials.gov/definitions.html
  - Required data elements fall under 12 broad categories:



Study Information

Study Identification

Unique Protocol ID: Sponsor identifier
Brief Title: Short title in lay terms
Official Title: Protocol Name
Secondary IDs:

Study Status

Record Verification: February 2023
Overall Status: Not yet recruiting
Study Start: April 2023 [Anticipated]
Primary Completion: May 2024 [Anticipated]
Study Completion: September 2024 [Anticipated]

Sponsor/Collaborators

Sponsor: Children's Hospital Medical Center, Cincinnati
Responsible Party: Sponsor
Collaborators:

Oversight

U.S. FDA-regulated Drug: Yes
U.S. FDA-regulated Device: No
U.S. FDA IND/IDE: Yes
IND/IDE Information:
FDA Center: CBER
IND/IDE Number:
IND Serial Number:
Has Expanded Access: No

Tips

- Use data element definitions guide to complete the entry fields
- Define acronyms
- Use realistic estimate for anticipated study start date
- Brief summary should be in lay terms and can be a helpful tool for recruiting.

Study Description

Brief Summary: Describe the study and hypothesis

Detailed Description: Technical description of study

Conditions

Conditions: Disease
Keywords:

Study Design

Study Design

Study Type:	Interventional [Change...]
Primary Purpose:	Treatment
Study Phase:	Phase 2
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	Triple (Participant, Care Provider, Investigator)
Allocation:	Randomized
Enrollment:	40 [Anticipated]

Tips

- **Study type: Interventional, Observational, Expanded Access**
- **If your study does not conform to any study model choices, contact PRS support for advice.**
- **Models for observational studies are in the data element definitions**

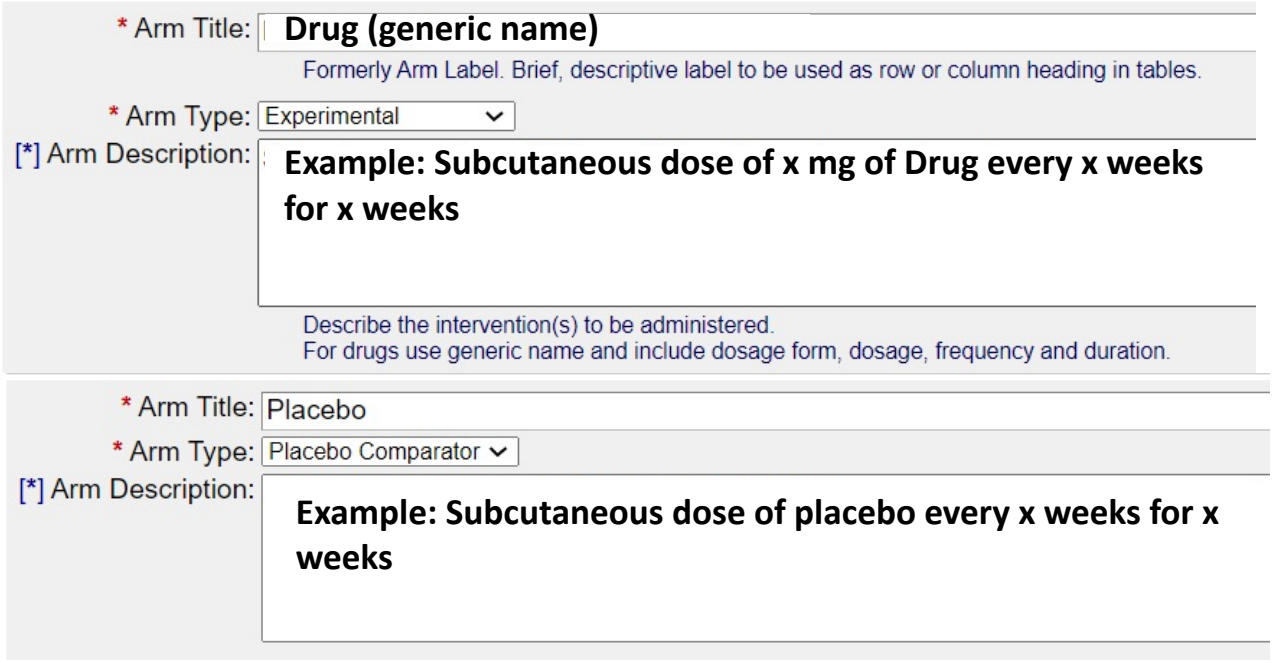
Definitions

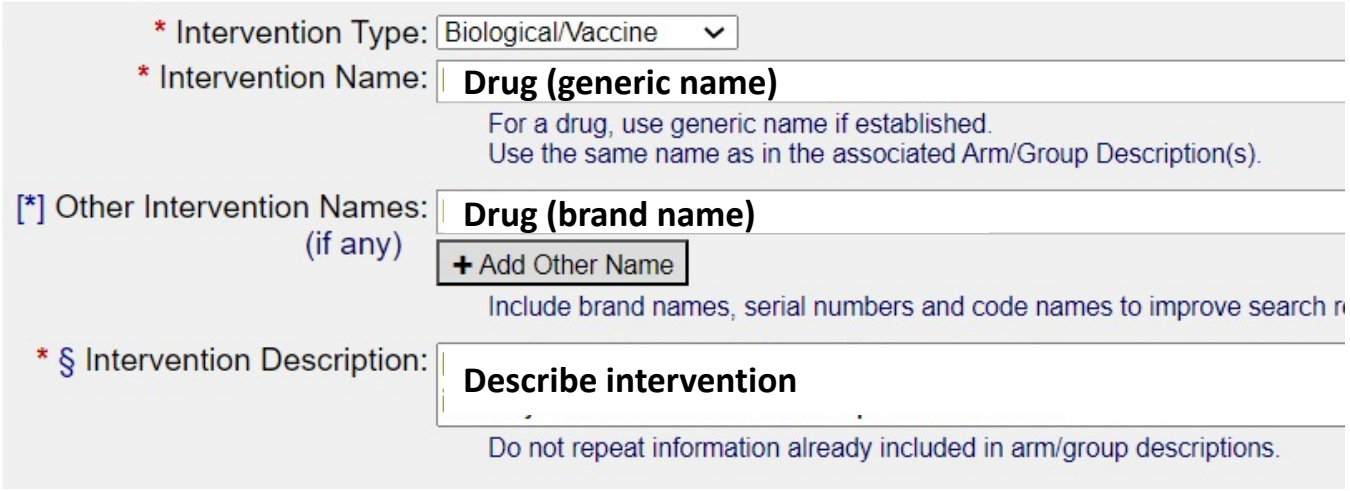
Interventional Study Model *§

Definition: The strategy for assigning interventions to participants.

- Single Group: Clinical trials with a single arm
- Parallel: Participants are assigned to one of two or more groups in parallel for the duration of the study
- Crossover: Participants receive one of two (or more) alternative interventions during the initial phase of the study and receive the other intervention during the second phase of the study
- Factorial: Two or more interventions, each alone and in combination, are evaluated in parallel against a control group
- Sequential: Groups of participants are assigned to receive interventions based on prior milestones being reached in the study, such as in some dose escalation and adaptive design studies

Arms & Interventions





Tip

- **Describe arm: dosage form, dosage, frequency, and duration**

Definitions

Arm Type *

Definition: The role of each arm in the clinical trial.

- Experimental
- Active Comparator
- Placebo Comparator
- Sham Comparator
- No Intervention
- Other

Tip

- **For intervention description, do not repeat the arm description (Arm Type, however, should match Intervention name)**

Arms and Interventions

- If study design is “parallel” interventional treatment with 2 arms:

Arms and Interventions

Arms	Assigned Interventions
Experimental: **Drug (generic name)** **Arm description**	Biological/Vaccine: **Drug (generic name)** **Description of intervention** Other Names: • **Drug (brand name)**
Placebo Comparator: Placebo **Arm description**	Biological/Vaccine: Placebo **Description of intervention**

- If study design is “single group assignment” interventional treatment with 1 arm:

Arms and Interventions

Arms	Assigned Interventions
Experimental: **Drug (generic name)** **Arm description**	Drug: **Drug (generic name)** **Description of intervention** Other Names: • **Drug (brand name)**

Outcome Measures, Eligibility, and Data Sharing

Outcome Measures

Primary Outcome Measure:

1. **Primary outcome**

Description

Secondary Outcome Measures:

3. **Secondary outcomes**

Description

Eligibility

Minimum Age: 18 Years

Maximum Age: 70 Years

Sex: All

Gender Based: No

Accepts Healthy Volunteers: No

Criteria:

Inclusion Criteria:

Plan to Share IPD

Definition: Indicate whether there is a plan to make individual participant data (IPD) (typically after the end of the study). Select one.

- Yes: There is a plan to make IPD and related data dictionaries available.
- No: There is not a plan to make IPD available.
- Undecided: It is not yet known if there will be a plan to make IPD available.

Tips

- **Clearly stated study protocol outcomes will make this entry significantly easier**
- **Primary, secondary, and pre-specified outcomes (exploratory) should be entered (Note: exploratory RESULTS are not required).**
- **All inclusion and exclusion criteria must be entered**
- **Sharing statement must align with the consent**

Maintenance of Record

Tips & Requirements

- Updates to a record can be made at ANY time
- Changes reflective of protocol amendments must be made at least every 12 months
  - Recommend sooner if significant to inclusion/exclusion
- Record Verification date should be updated every 6 months even if no changes are made

Required Registration Updates

Responsible Parties should update their records within 30 days of a change to any of the following:

- Recruitment Status and Overall Recruitment Status data elements on ClinicalTrials.gov
- Completion Date (See Primary Completion Date data element on ClinicalTrials.gov)

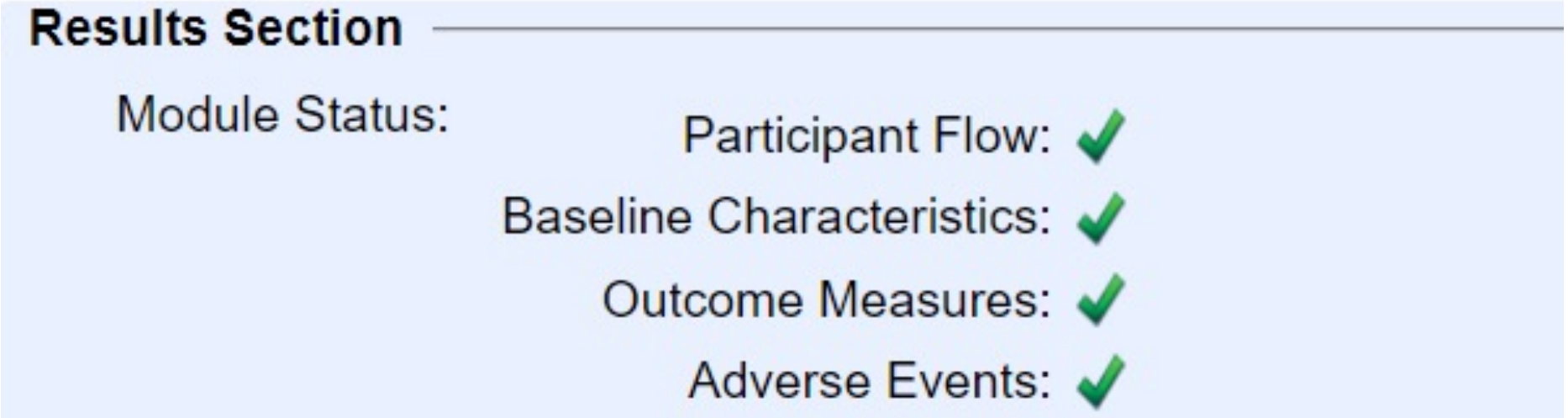
Tips for Record Maintenance

- Annual Verification
  - Consider checking in with annual IRB Continuing Reviews or other annual updates (i.e. Grant reporting or FDA reporting)
- Major Modifications
  - FDA approval or clearance of drug/biologic/device under study
  - Responsible Party changes
  - Individual Site Status changes
- Status Updates:
  - Enrollment, completed, withdrawn, terminated, etc.
  - Study dates: Start Date, Primary Completion, Study Completion

Submitting Results

- Similar to preparing a manuscript for publication.
- **Best Practice:** An individual familiar with the study design and data analysis should be involved in order to accurately summarize the results.

- Enter the required data elements:
  https://clinicaltrials.gov/ct2/manage-recs/how-report
  https://prsinfo.clinicaltrials.gov/results_definitions.html
  - Required results fall under 4 broad categories:



Participant Flow

Identical in purpose to CONSORT Diagram but in table form

Recruitment Information

Significant events following enrollment, but prior to assignment
400 participants were screened. 175 did not meet criteria.

Participant Flow: Treatment Initial Randomization (Period 1)

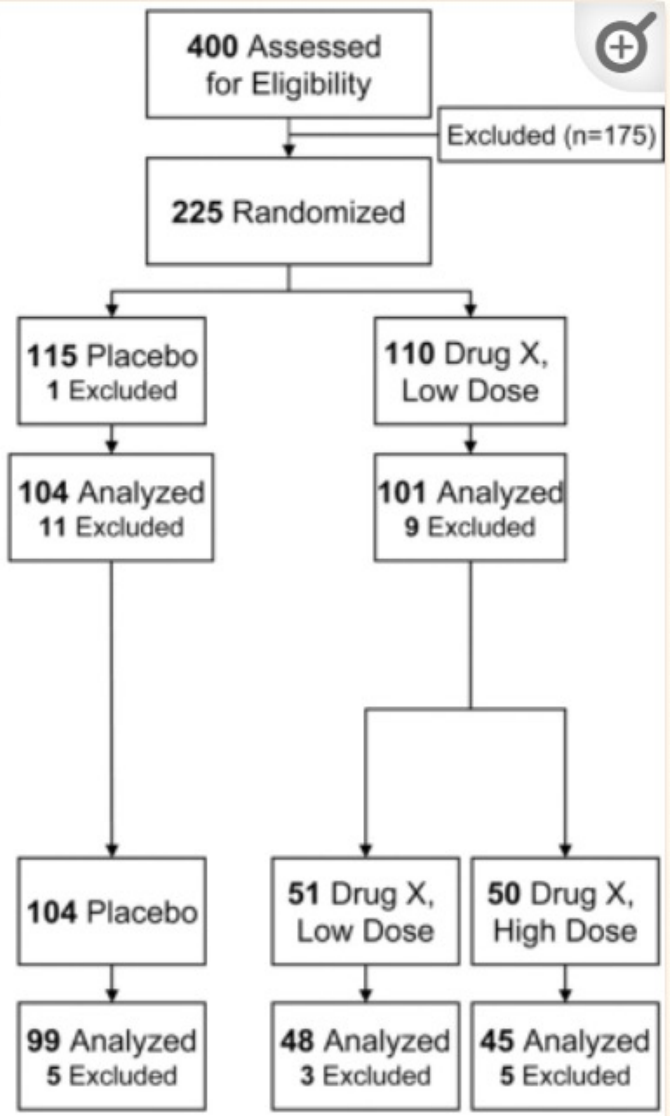
Arm/Group

Milestone	Placebo	Drug X, Low Dose	Drug X, High Dose
STARTED	115	110	0
Received Intervention	114	110	0
COMPLETED	104	101	0
NOT COMPLETED	11	9	0
Adverse Event	4	5	0
Lost to Follow-up	4	2	0
Neutropenia	3	2	0

Participant Flow: Treatment Re-Randomization (Period 2)

	Placebo	Drug X, Low Dose	Drug X, High Dose
STARTED	104	51	50
COMPLETED	99	48	45
NOT COMPLETED	5	3	5
Lost to Follow-up	2	2	5
Neutropenia	3	1	0

"Customized" Reason for Non-completion



Chest. 2009 Jul; 136(1): 295–303

Participant Flow

Participant Flow Template — *ClinicalTrials.gov*

Recruitment Details	
[*] Pre-assignment Details	

Period ①

* Period Title	Overall Study ①			
* Arm/Group Title				
*§ Arm/Group Description ②				
		Number of Participants ④	Number of Participants ④	Number of Participants ④
* Started				
[*] Milestone Title ③				
[*] Milestone Title ③				
[*] Milestone Title ③				
* Completed				
Not Completed		*(automatically calculated)*		
Reason Not Completed Type ③				
[*] Adverse Event				
[*] Death				
[*] Lack of Efficacy				
[*] Lost to Follow-up				
[*] Physician Decision				
[*] Pregnancy				
[*] Protocol Violation				
[*] Withdrawal by Subject				
[*] Other Reason				
[*] Other Reason				
[*] Other Reason				

* Required *§ Required if Primary Completion Date is on or after January 18, 2017 [*] Conditionally required

Tip

- Use templates to help prepare for the data entry

Baseline Characteristics

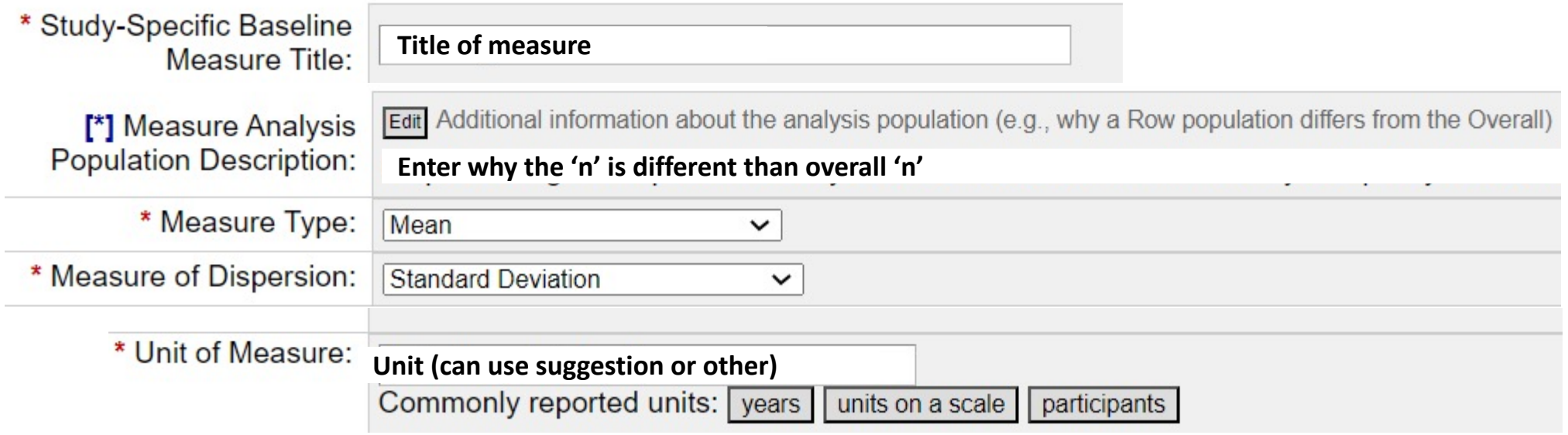
- **4 categories of characteristics are required**
  - Age (continuous, categorical, or customized)
  - Sex/gender
  - Race and ethnicity
  - Study specific measures*

Tip:

- ***Most outcomes will have a baseline study specific measure entered Note: PRS will flag an outcome that is "change from baseline" and no baseline value is entered here**

Baseline Characteristics

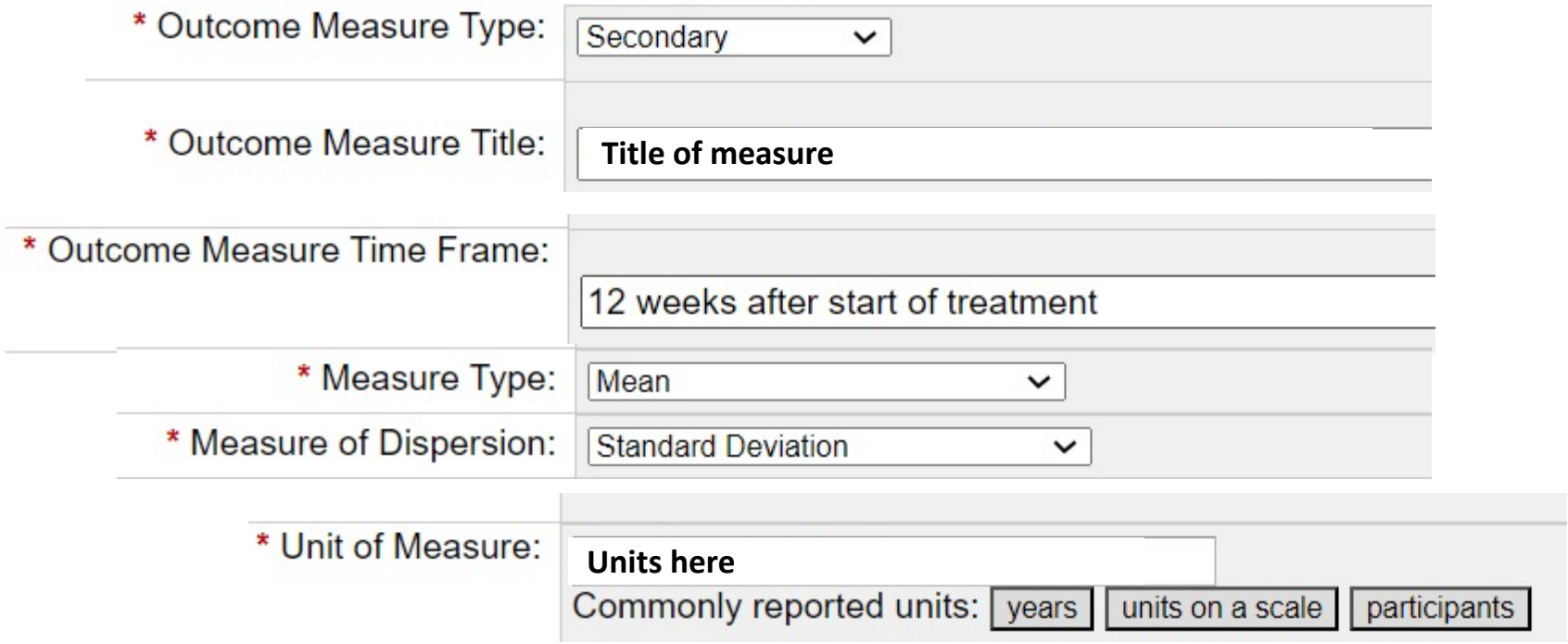
Key data elements



Tips:

- If the 'n' for a measure differs from the overall 'n', this must be explained.
- All entries require a measure type and dispersion (statistician input is essential)
- Acronyms must be defined
- Entries should be consistent with the statistical analysis plan

Outcomes & Statistical Analysis



Tips:

- **Data should use same terms, measure type and dispersion as baseline characteristics**
- **Keep titles simple (can be changed from outcomes entered when registering if too detailed)**
- **Primary and secondary outcome results are required; other outcomes are optional**

Outcomes

Outcome Measure Template Example 1 (Units=Participants; Measure Type=Count of Participants; Measure of Dispersion/Precision=Not Applicable) ***ClinicalTrials.gov***

* Outcome Measure Type	(Select One) (Primary) Secondary Other Pre-specified Post-Hoc
* Outcome Measure Title	**Number of Participants With Myocardial Infarction, Stroke or Death From Cardiovascular Causes**
[*] Outcome Measure Description	Participants were monitored for up to 2 years. This is the number of participants who have had at least one myocardial infarction or stroke, or if they died from cardiovascular causes during the time of observation.
* Outcome Measure Time Frame	Up to 2 years

* Arm/Group Title		**Low-dose Aspirin Therapy**		**Beta Blocker Therapy**		
*§ Arm/Group Description ①		Participants with familial history of cardiovascular disease received 81 mg Aspirin once daily		Participants with familial history of cardiovascular disease received 100 mg Beta Blocker once daily		
* Overall Number of Participants Analyzed		**1,545**		**1,524**		
[*] Analysis Population Description		All participants who received at least one dose of treatment.				
* Measure Type	* Measure of Dispersion/Precision					
(Select One) (Count of Participants ②) Mean Median Least Squares Mean (LSM) Geometric Mean Geometric LSM Number Count of Units	(Select One) (Not Applicable ③) Standard Deviation Standard Error Inter-Quartile Range Full Range _____ % Confidence Interval Geometric Coefficient of Variation	**277**	②③	**246**	②③	②③
* Unit of Measure	Participants					

* Required *§ Required if Primary Completion Date is on or after January 18, 2017 [*] Conditionally required

Tip

- **Use templates to help prepare for the data entry**

Outcomes & **Statistical Analysis**

Statistical Analysis Template ***ClinicalTrials.gov***

Statistical Analysis Overview	* Comparison Group Selection ①	☐ Arm/Group 1 ☐ Arm/Group 2 ☐ Arm/Group 3
	Comments ②	
	* Type of Statistical Test	**(Select One)** Superiority; Equivalence; Non-inferiority; Other (for example, single group or other descriptive analysis)
	[*] Comments ③	
Statistical Test of Hypothesis	[*] P-Value (if applicable)	_____ *(calculated value, not the a priori threshold for statistical significance)*
	Comments ②	
	[*] Method (required if p-value entered)	**(Select One)** ANCOVA; ANOVA; Chi-Squared; Chi-Squared, Corrected; Cochran-Mantel-Haenszel; Fisher Exact; Kruskal-Wallis; Log Rank; Mantel Haenszel; McNemar; Mixed Models Analysis; Regression, Cox; Regression, Linear; Regression, Logistic; Sign Test; t-Test, 1-Sided; t-Test, 2-Sided; Wilcoxon (Mann-Whitney); Other (_____)
	Comments ②	
Method of Estimation	[*] Estimation Parameter (if applicable)	**(Select One)** Cox Proportional Hazard; Hazard Ratio (HR); Hazard Ratio, Log; Mean Difference (Final Values); Mean Difference (Net); Median Difference (Final Values); Median Difference (Net); Odds Ratio (OR); Odds Ratio, Log; Risk Difference (RD); Risk Ratio (RR); Risk Ratio, Log; Slope; Other (_____)
	Estimated Value	_____ *(calculated value)*
	Confidence Interval (if applicable)	**Level:** _____ % Confidence Interval **Number of Sides: (Select One)** 2-sided 1-sided **Lower Limit:** _____ **Upper Limit:** _____
	Parameter Dispersion	**Type: (Select One)** Standard Deviation; Standard Error of the Mean **Value:** _____
	Estimation Comments ②	
Other Statistical Analysis ④		

Tips

- **Statistical analysis should match statistical analysis plan**
- **Critical for statistician or knowledgeable investigator to be involved**
- **Every outcome requires an analysis entry**

Adverse events

All-Cause Mortality

Serious Adverse Events

Other (Not Including Serious) Adverse Events

Frequency Threshold for Reporting Other Adverse Events

- **Need number affected, overall number at risk, AE term, Organ System, how AEs were collected.**
- **Can define a frequency threshold (e.g., 5%) for AEs to limit data entry to the most relevant events**

Summary

- Frequently refer to data element definitions guide for data entry
- Collaborate with study team to complete registration and submit results
  - Study team = investigators, coordinator AND statistician
- Give yourself ample time for entry
- Don’t be hesitant to contact PRS with questions
- Review examples of various study types: https://clinicaltrials.gov/ct2/manage-recs/present