NIH and Other Requirements for ClinicalTrials.gov Reporting

NIH Pragmatic Trials Collaboratory Steering Committee Meeting May 17, 2023

Stacey Arnold, PhD
Results Team Subject Matter Expert, ClinicalTrials.gov

National Library of Medicine

Topics

- ClinicalTrials.gov Reporting Requirements
- Modernization Effort
- Recommendations for Pragmatic Clinical Trials

ClinicalTrials.gov Reporting Requirements

Why Register and Report Results?

- **Required by medical journals**
  - Registration for all clinical trials (all interventions)
- **Federal regulations (42 CFR Part 11: “Final Rule”)**
  - Registration & results information submission for “applicable clinical trials”
  - Federal law (FDAAA 801): in effect since 2007; Final Rule: in effect January 18, 2017
- **Expectation for NIH-supported trials**
  - Registration & results submission, even if not subject to 42 CFR Part 11
  - Policy effective January 18, 2017

Benefits of Comprehensive Registration and Results Reporting

All contribute to increased public trust in clinical research

- Honor commitment to participants that their contributions will advance science; support enrollment
- Mitigate publication bias
- Advance stewardship and accountability
  - Identify unmet research needs
  - Facilitate complete reporting
  - Avoid unnecessary study duplication
  - Evaluate research integrity
- Support evidence-based medicine

General Requirements: Final Rule

The Responsible Party for an Applicable Clinical Trial (ACT) must:

1. **Register** the ACT in ClinicalTrials.gov no later than 21 days after enrollment of the first participant
2. **Update** the ACT in ClinicalTrials.gov at least once every 12 months (some information within 15 or 30 days of change)
3. **Submit summary results** (including adverse events) for certain ACTs not later than 1 year after the trial's Primary Completion Date
   - Delays allowed in some circumstances

General Requirements: NIH Policy

- Necessitates reporting of all NIH-funded clinical trials (not just “applicable clinical trials”)
  - Applies to applications for funding submitted on or after January 18, 2017 for clinical trials initiated on or after January 18, 2017
- “For those covered by the NIH policy only, NIH-funded awardees and investigators will be expected to submit the same registration and results information in the same timeframes as those subject to the statute and rule”

Registration, Results Submission and Publication

- Deadline for submitting results to ClinicalTrials.gov is independent of publication status
- Submitting results to ClinicalTrials.gov will not interfere with publication
  - Failure to register WILL interfere with publication!
- ClinicalTrials.gov records are linked, via NCT number, to publications
  - Ensure the registration record is up-to-date

Clarifications about Results Reporting Requirements

- Does NOT prescribe how study should be conducted
- Summary results at the end of the trial
  - No interim or “real time” reporting; no participant level reporting
- Information currently targeted at readers of the medical literature
  - “Tables” of information/“just the facts”; no conclusions or discussion
- Results submission is not required for registered studies that are not subject to 42 CFR Part 11 or NIH Policy
  - For example, if not studying an FDA-regulated product and no NIH funding
  - Although other funding policy might require results submission

ICMJE and Data Sharing
(*Ann Intern Med. 2017 Jul 4;167(1):63-65.*)

- ICMJE requires the following as a condition of publication of results of clinical trials
  - Manuscripts must contain a data sharing statement (July 1, 2018)
  - Clinical trial registration must include a data sharing plan (clinical trials that begin enrolling participants on or after January 1, 2019)
- Initial requirements do not yet mandate data sharing
  - Editors may take into consideration data sharing statements when making editorial decisions

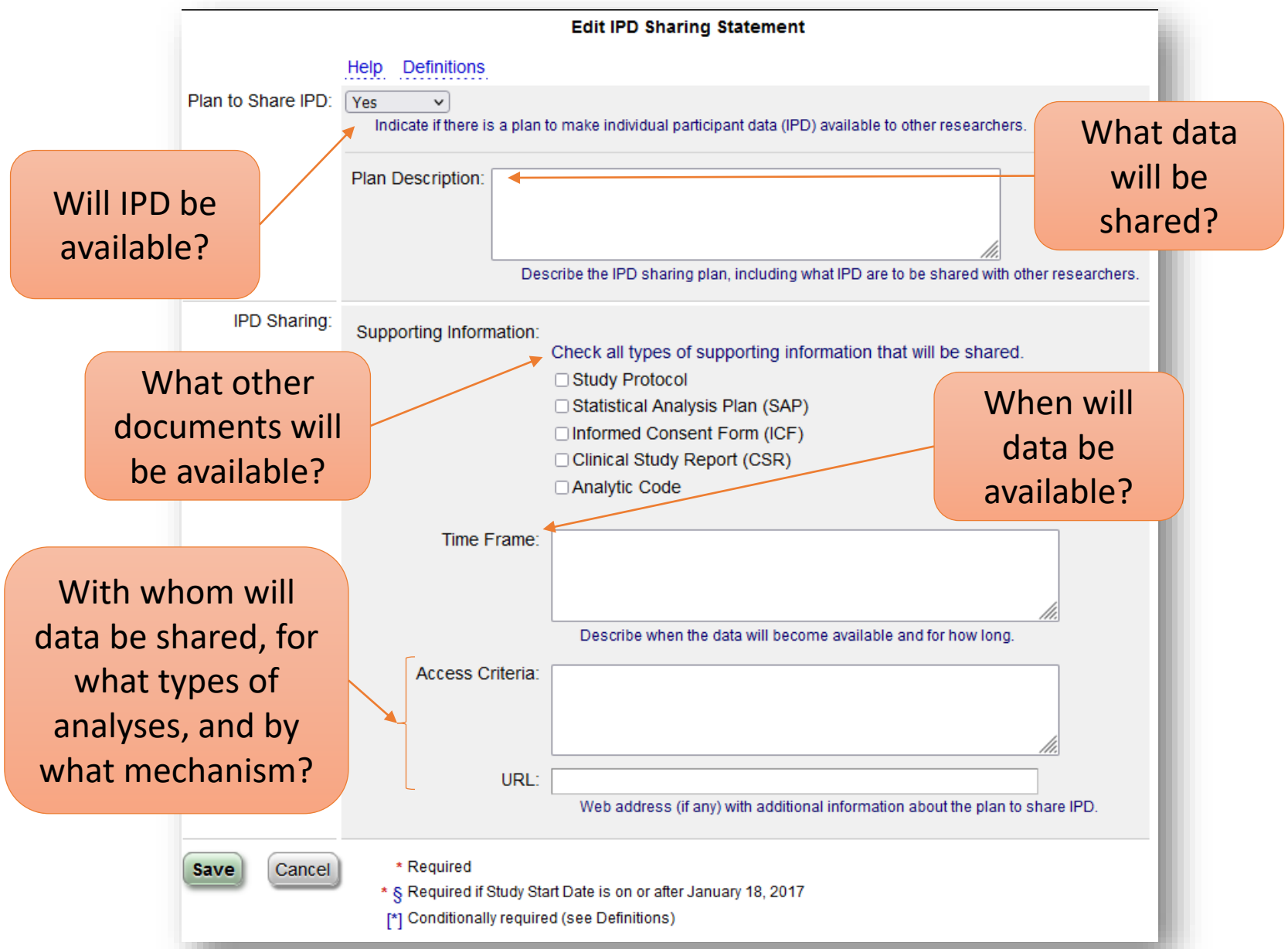
Data Sharing Statement – ICMJE June 2017

- Data sharing statements must include:
  - Whether individual de-identified participant data will be shared
  - What data will be shared
  - Whether related documents will be available (e.g., protocol)
  - When the data will become available
  - By what access criteria data will be shared

- ClinicalTrials.gov Data Elements (June 29, 2017)
  - Plan to Share IPD (Yes, No, Undecided)
  - Plan Description
  - Supporting Information Type
  - Time Frame
  - Access Criteria
  - URL (for more information about sharing plan)

Individual Participant Data (IPD) – IPD Sharing Statement Module

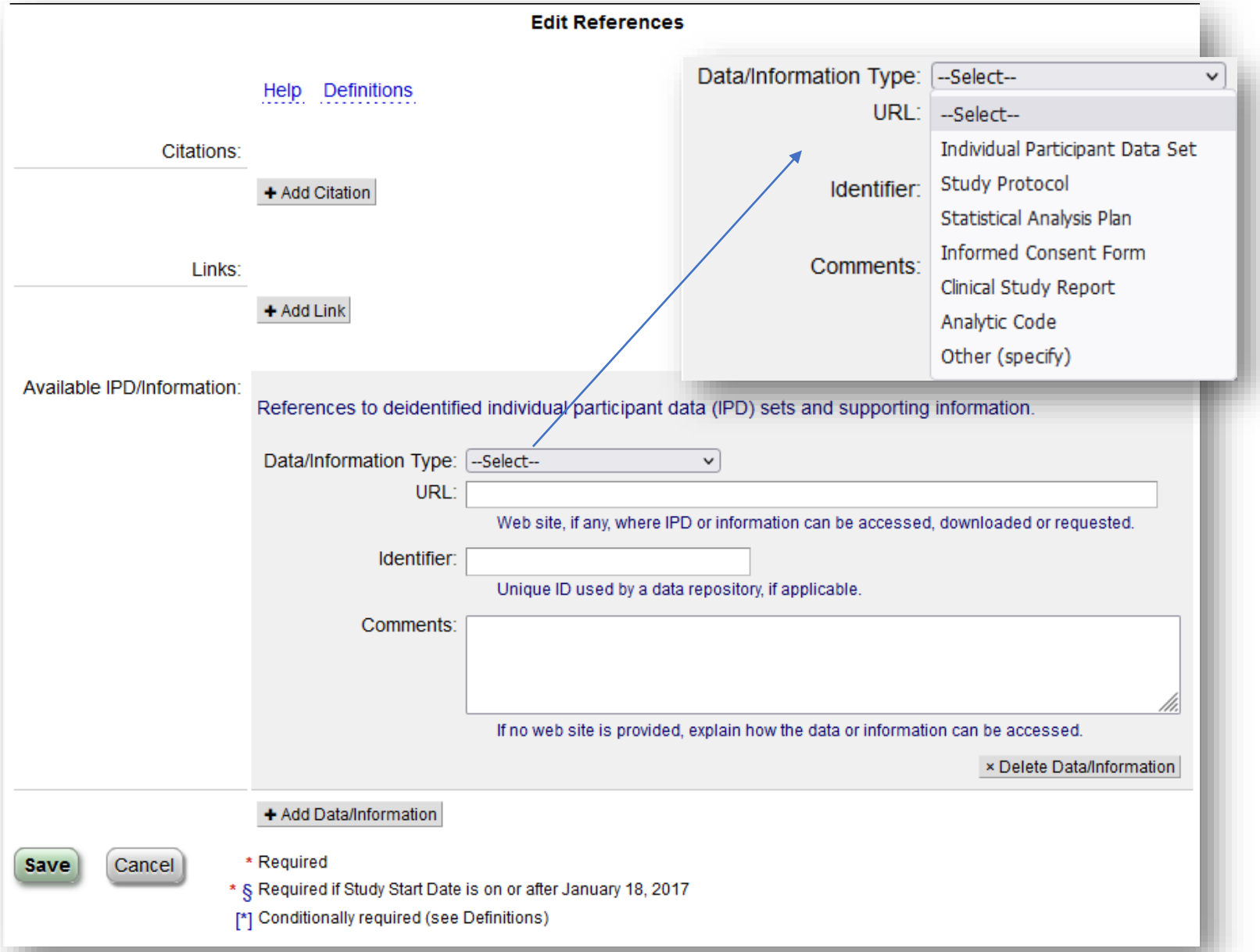
The IPD Sharing Statement Module is in the Protocol Registration and Results System (PRS), the database used to enter trial information for publication to ClinicalTrials.gov.



Individual Participant Data (IPD) – References Module

Users can provide access information for:

- *The data set*
- *The supporting information promised in the IPD Sharing Statement Module*



Modernization Effort

Users Are Central to Approach

Patients and Their Advocates

Data Submitters

Data Researchers

Defined User Needs

Over 250 RFI (Request for Information) responses about PRS information submission, website functionality, and data standards

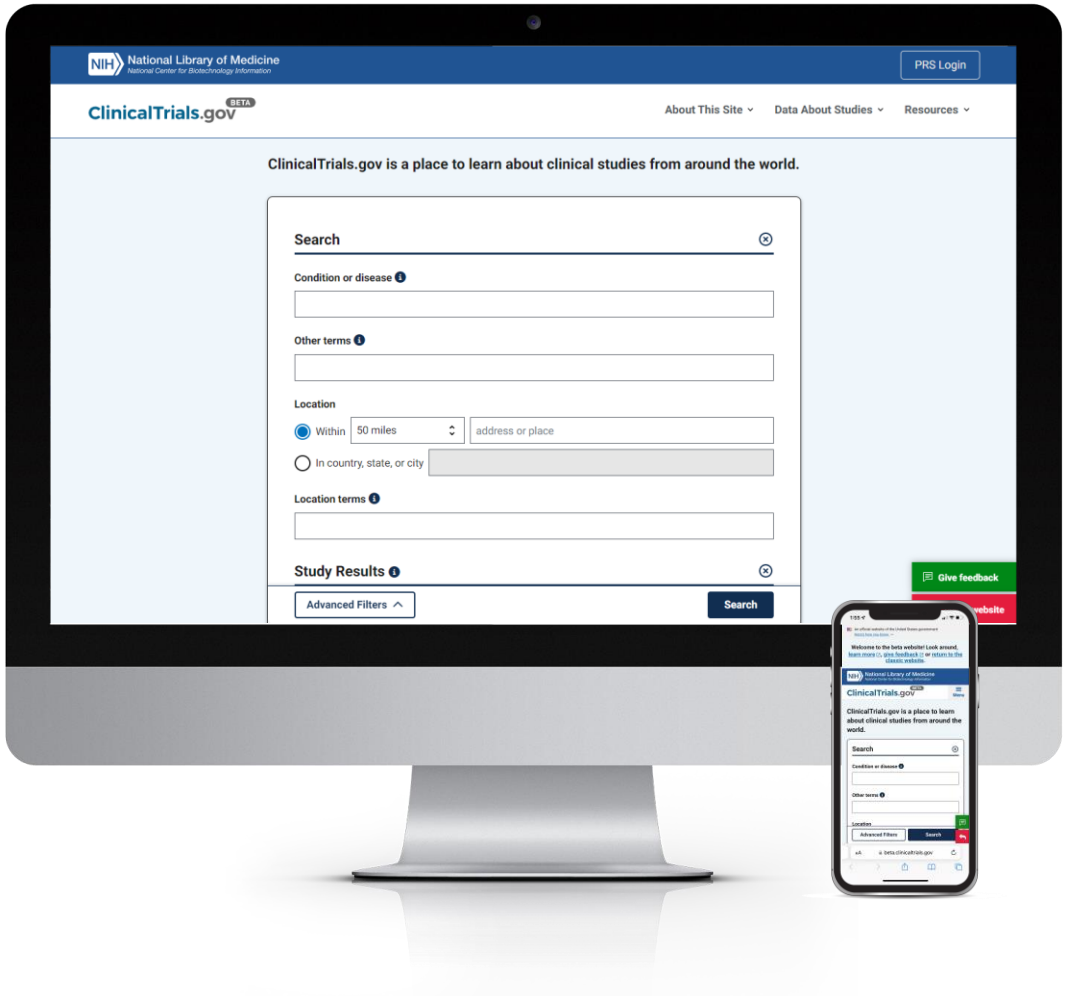
Identified Design Opportunities

Over 70 individual interviews with people representing the three primary user groups

Evaluated Design with Users

Multiple rounds of individual users providing feedback on wireframes and prototypes

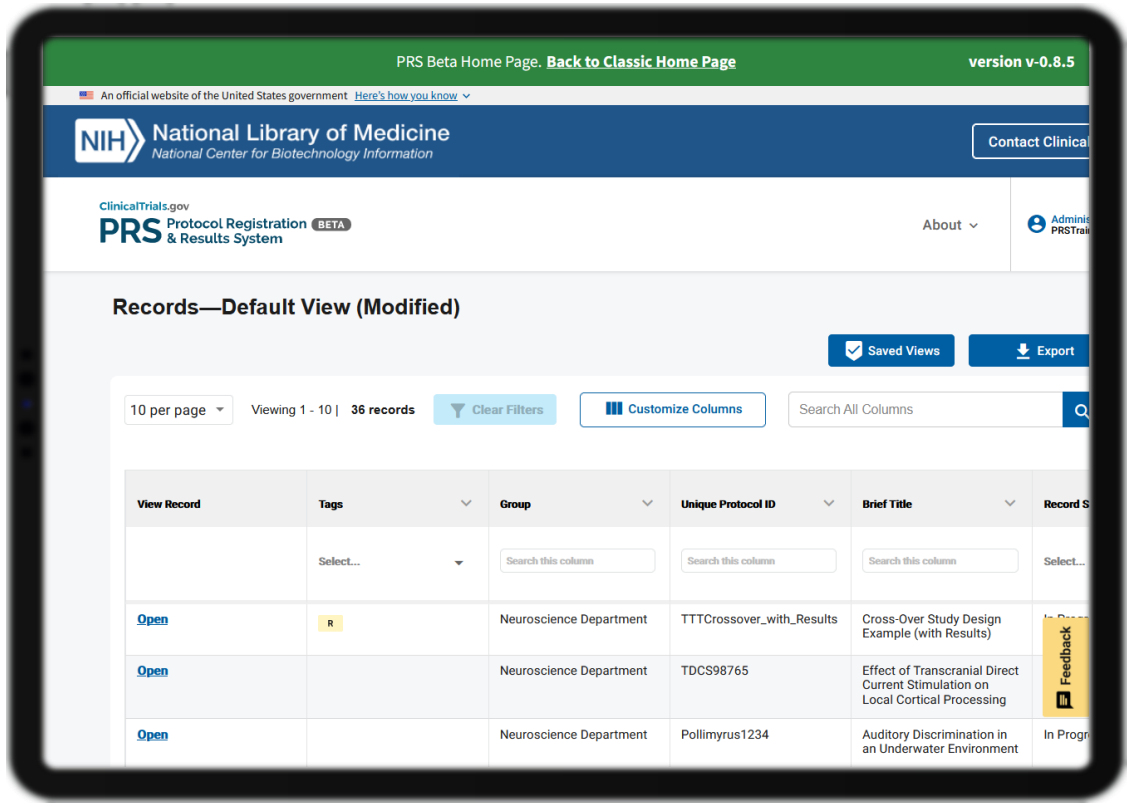
Initial ClinicalTrials.gov Beta Releases



Key Features

- Modern look and feel
- Ease of use on mobile device
- Easy-to-understand information
- New cloud-based infrastructure

Initial PRS Beta Releases



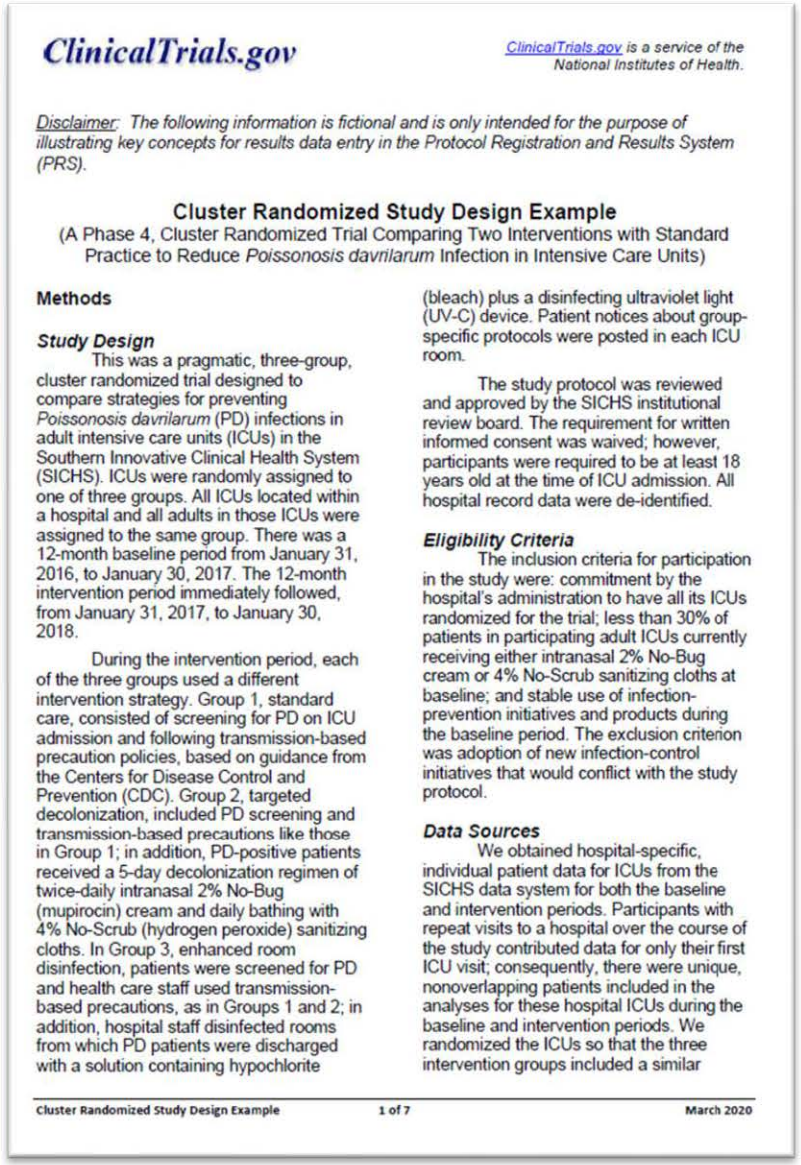
Key Features

- Modern and intuitive design
- Ability to email study staff directly from the Record List
- Customizable display
  - Reorder, add, and hide columns
  - Apply multicolumn filters
- Available for download in Microsoft Excel and CSV formats

Recommendations for Pragmatic Clinical Trials

Cluster Randomized Study Design Example

https://clinicaltrials.gov/ct2/manage-recs/present#ResultsExamplStudies



ClinicalTrials.gov

ClinicalTrials.gov is a service of the National Institutes of Health.

Disclaimer: *The following information is fictional and is only intended for the purpose of illustrating key concepts for results data entry in the Protocol Registration and Results System (PRS).*

Cluster Randomized Study Design Example

(A Phase 4, Cluster Randomized Trial Comparing Two Interventions with Standard Practice to Reduce *Poissonosis davrilarum* Infection in Intensive Care Units)

Methods

Study Design

This was a pragmatic, three-group, cluster randomized trial designed to compare strategies for preventing *Poissonosis davrilarum* (PD) infections in adult intensive care units (ICUs) in the Southern Innovative Clinical Health System (SICHS). ICUs were randomly assigned to one of three groups. All ICUs located within a hospital and all adults in those ICUs were assigned to the same group. There was a 12-month baseline period from January 31, 2016, to January 30, 2017. The 12-month intervention period immediately followed, from January 31, 2017, to January 30, 2018.

During the intervention period, each of the three groups used a different intervention strategy. Group 1, standard care, consisted of screening for PD on ICU admission and following transmission-based precaution policies, based on guidance from the Centers for Disease Control and Prevention (CDC). Group 2, targeted decolonization, included PD screening and transmission-based precautions like those in Group 1; in addition, PD-positive patients received a 5-day decolonization regimen of twice-daily intranasal 2% No-Bug (mupirocin) cream and daily bathing with 4% No-Scrub (hydrogen peroxide) sanitizing cloths. In Group 3, enhanced room disinfection, patients were screened for PD and health care staff used transmission-based precautions, as in Groups 1 and 2; in addition, hospital staff disinfected rooms from which PD patients were discharged with a solution containing hypochlorite (bleach) plus a disinfecting ultraviolet light (UV-C) device. Patient notices about group-specific protocols were posted in each ICU room.

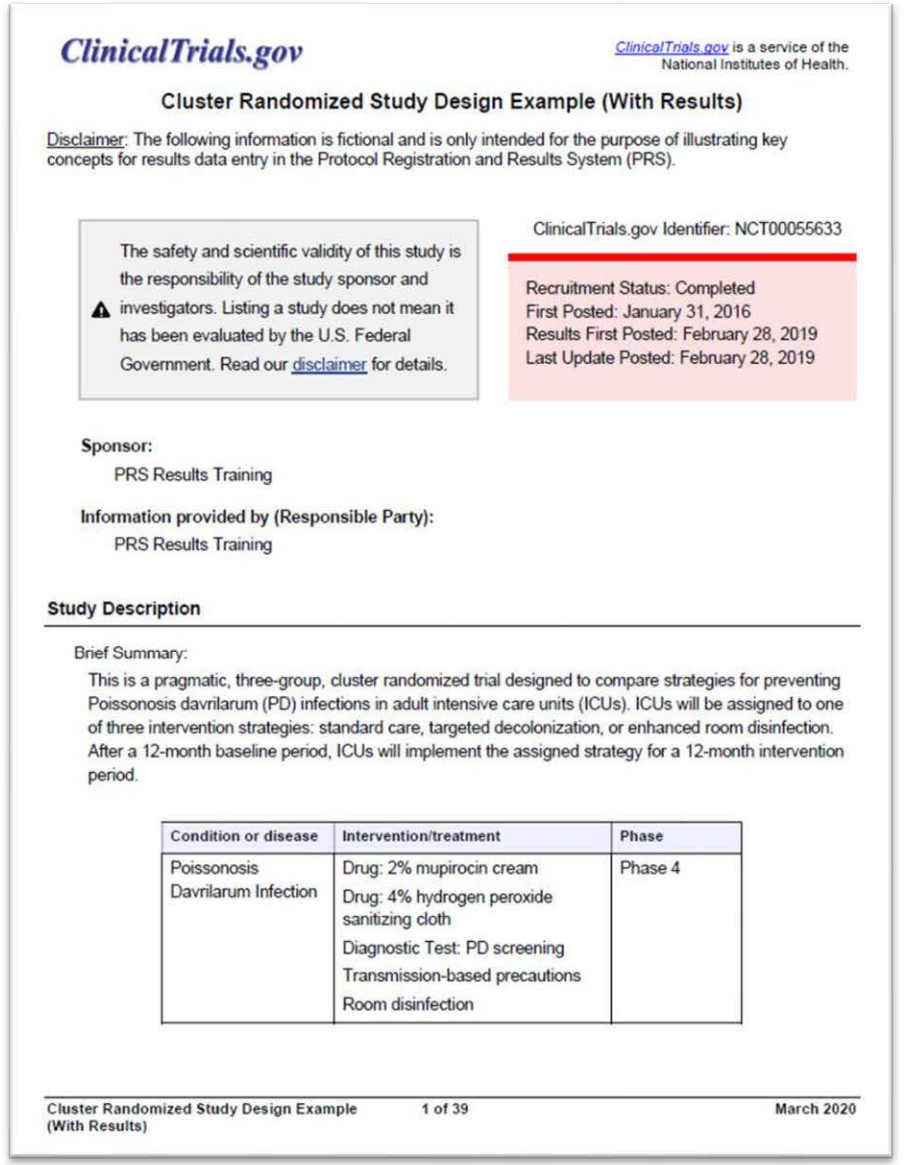
The study protocol was reviewed and approved by the SICHS institutional review board. The requirement for written informed consent was waived; however, participants were required to be at least 18 years old at the time of ICU admission. All hospital record data were de-identified.

Eligibility Criteria

The inclusion criteria for participation in the study were: commitment by the hospital's administration to have all its ICUs randomized for the trial; less than 30% of patients in participating adult ICUs currently receiving either intranasal 2% No-Bug cream or 4% No-Scrub sanitizing cloths at baseline; and stable use of infection-prevention initiatives and products during the baseline period. The exclusion criterion was adoption of new infection-control initiatives that would conflict with the study protocol.

Data Sources

We obtained hospital-specific, individual patient data for ICUs from the SICHS data system for both the baseline and intervention periods. Participants with repeat visits to a hospital over the course of the study contributed data for only their first ICU visit; consequently, there were unique, nonoverlapping patients included in the analyses for these hospital ICUs during the baseline and intervention periods. We randomized the ICUs so that the three intervention groups included a similar



ClinicalTrials.gov

ClinicalTrials.gov is a service of the National Institutes of Health.

Cluster Randomized Study Design Example (With Results)

Disclaimer: The following information is fictional and is only intended for the purpose of illustrating key concepts for results data entry in the Protocol Registration and Results System (PRS).

⚠ The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT00055633

Recruitment Status: Completed
First Posted: January 31, 2016
Results First Posted: February 28, 2019
Last Update Posted: February 28, 2019

Sponsor:
PRS Results Training

Information provided by (Responsible Party):
PRS Results Training

Study Description

Brief Summary:
This is a pragmatic, three-group, cluster randomized trial designed to compare strategies for preventing Poissonosis davrilarum (PD) infections in adult intensive care units (ICUs). ICUs will be assigned to one of three intervention strategies: standard care, targeted decolonization, or enhanced room disinfection. After a 12-month baseline period, ICUs will implement the assigned strategy for a 12-month intervention period.

Condition or disease	Intervention/treatment	Phase
Poissonosis Davrilarum Infection	Drug: 2% mupirocin cream Drug: 4% hydrogen peroxide sanitizing cloth Diagnostic Test: PD screening Transmission-based precautions Room disinfection	Phase 4

Units Assigned – Participant Flow

Recruitment Details	201 ICUs in 140 SICHS hospitals were screened.
Pre-assignment Details	78 ICUs in 45 hospitals were randomized; 4 were excluded before the baseline period (met the exclusion criterion). All ICUs in a hospital and all adults in those ICUs were assigned to the same group. Participants were counted only once during the study (first ICU visit) and did not overlap in the baseline and intervention periods.

Arm/Group Title	Group 1: Standard Care	Group 2: Targeted Decolonization Plus Standard Care	Group 3: Enhanced Room Disinfection Plus Standard Care
▸ Arm/Group Description	Patients were screened for Poissono...	As in Group 1, patients were screen...	As in Groups 1 and 2, patients were...

Period Title: **Baseline Period: Months 1-12**

Type Units Assigned: Intensive Care Units	Number of participants	Number of units (Intensive Care Units)	Number of participants	Number of units (Intensive Care Units)	Number of participants	Number of units (Intensive Care Units)
Started	39530	23	41229	22	38804	29
Completed	39530	23	41229	22	38804	29
Not Completed	0	0	0	0	0	0

Number of participants assigned

Number of units assigned

Clusters should be added to the participant flow table, alongside participants, to fully represent assignment in each arm.

Units Analyzed – Baseline

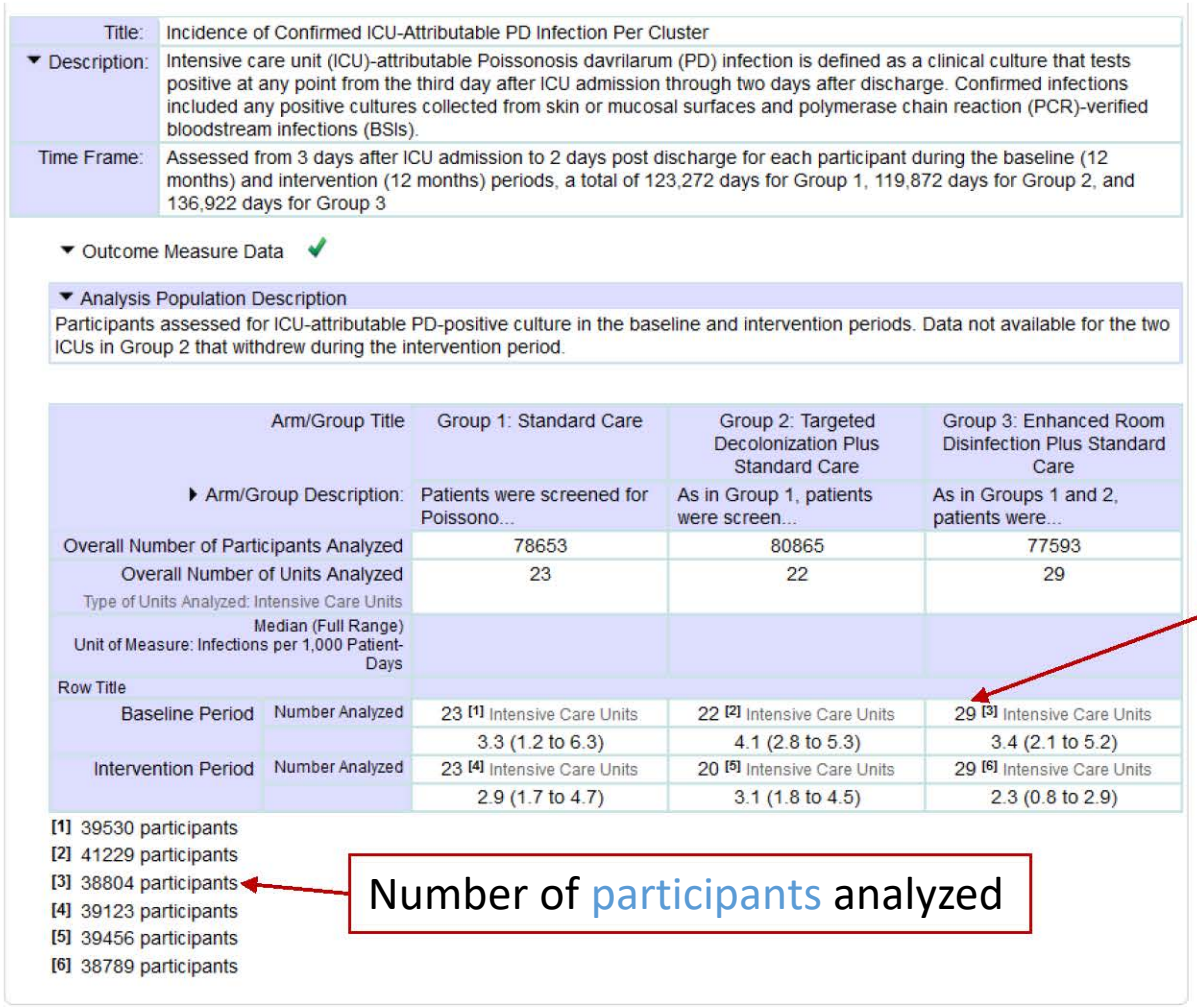
Arm/Group Title		Group 1: Standard Care		Group 2: Targeted Decolonization Plus Standard Care		Group 3: Enhanced Room Disinfection Plus Standard Care		Total	
Intensive Care Unit Type [1] Measure Type: Count of Units Unit of measure: Intensive Care Units		Number of units analyzed							
Baseline Period	Number Analyzed	23 [2] Intensive Care Units		22 [3] Intensive Care Units		29 [4] Intensive Care Units		74 [5] Intensive Care Units	
	Medical Only	3	13.04%	3	13.64%	2	6.9%	8	10.81%
	Surgical Only	2	8.7%	4	18.18%	3	10.34%	9	12.16%
	Medical and Surgical	18	78.26%	15	68.18%	24	82.76%	57	77.03%
Intervention Period	Number Analyzed	23 [6] Intensive Care Units		20 [7] Intensive Care Units		29 [8] Intensive Care Units		72 [9] Intensive Care Units	
	Medical Only	3	13.04%	1	5%	2	6.9%	6	8.33%
	Surgical Only	2	8.7%	4	20%	3	10.34%	9	12.5%
	Medical and Surgical	18	78.26%	15	75%	24	82.76%	57	79.17%

[1] Measure Analysis Population Description: Data not available for the two ICUs in Group 2 that withdrew during the intervention period
[2] 39530 participants
[3] 41229 participants
[4] 38804 participants
[5] 119563 participants
[6] 39123 participants
[7] 39456 participants
[8] 38789 participants
[9] 117368 participants

Number of participants analyzed

Clusters can be added to data tables, alongside participants, to provide data at both levels.

Units Analyzed – Outcome Measure



Title:	Incidence of Confirmed ICU-Attributable PD Infection Per Cluster
▼ Description:	Intensive care unit (ICU)-attributable Poissonosis davrilarum (PD) infection is defined as a clinical culture that tests positive at any point from the third day after ICU admission through two days after discharge. Confirmed infections included any positive cultures collected from skin or mucosal surfaces and polymerase chain reaction (PCR)-verified bloodstream infections (BSIs).
Time Frame:	Assessed from 3 days after ICU admission to 2 days post discharge for each participant during the baseline (12 months) and intervention (12 months) periods, a total of 123,272 days for Group 1, 119,872 days for Group 2, and 136,922 days for Group 3

▼ Outcome Measure Data ✓

▼ Analysis Population Description

Participants assessed for ICU-attributable PD-positive culture in the baseline and intervention periods. Data not available for the two ICUs in Group 2 that withdrew during the intervention period.

Arm/Group Title		Group 1: Standard Care	Group 2: Targeted Decolonization Plus Standard Care	Group 3: Enhanced Room Disinfection Plus Standard Care
▶ Arm/Group Description:		Patients were screened for Poissono...	As in Group 1, patients were screen...	As in Groups 1 and 2, patients were...
Overall Number of Participants Analyzed		78653	80865	77593
Overall Number of Units Analyzed Type of Units Analyzed: Intensive Care Units		23	22	29
Median (Full Range) Unit of Measure: Infections per 1,000 Patient-Days				
Row Title				
Baseline Period	Number Analyzed	23 [1] Intensive Care Units	22 [2] Intensive Care Units	29 [3] Intensive Care Units
		3.3 (1.2 to 6.3)	4.1 (2.8 to 5.3)	3.4 (2.1 to 5.2)
Intervention Period	Number Analyzed	23 [4] Intensive Care Units	20 [5] Intensive Care Units	29 [6] Intensive Care Units
		2.9 (1.7 to 4.7)	3.1 (1.8 to 4.5)	2.3 (0.8 to 2.9)

[1] 39530 participants
[2] 41229 participants
[3] 38804 participants
[4] 39123 participants
[5] 39456 participants
[6] 38789 participants

Number of units analyzed

Number of participants analyzed

Clusters can be added to data tables, alongside participants, to provide data at both levels.

Note: This example is *not* in the Cluster Randomized Study Design Example paper.

Issues With Reporting

1. What if data can't be analyzed within a year of the **Primary Completion Date**?
   - It can take 1.5 years to analyze data collected via state or CMS health care services.
     - 3-6 months for claims processing
     - 1 year for creation and cleaning of analytic variables

Issues With Reporting – Data Not Analyzed in Time

What determines the Primary Completion Date?

- https://clinicaltrials.gov/ct2/manage-recs/faq#fr_29: “The Primary Completion Date is the date that the final study participant was examined or received an intervention for the purpose of the final collection of data for the primary outcome.”
- This is “the date of the examination or the administration of the intervention itself, not the date of any later assessment, analysis, or interpretation of the collected outcome… data.”

Issues With Reporting - Data Not Analyzed in Time

Good Cause Extension (GCE) request:

- New guidance is available at https://prsinfo.clinicaltrials.gov/20230112_GCE_Criteria_final_508.pdf
- The request should clarify the “impact of the circumstances leading to the GCE request, including steps the responsible party is taking to mitigate the impact of those circumstances,” and the “extent to which the factors underlying the GCE request are outside of the responsible party’s control.”
- The request should also provide an “estimated date on which the clinical trial results information will be submitted.”

Issues With Reporting

2. If a study only collects a pre-specified set of adverse events, how can this be represented?

Cluster Randomized Study Design Example

Adverse Events

Time Frame	Serious adverse events (SAEs): from intensive care unit (ICU) intake through 2 days after ICU discharge during the intervention period; Other (Not Including Serious) Adverse Events (OAEs): from 3 days after ICU intake through 2 days after ICU discharge
Adverse Event Reporting Description	Data on anticipated SAEs (sepsis, anaphylaxis, and bloodstream infection (BSI)-attributable deaths) were collected for all arms. All deaths were the result of BSIs. Only anticipated OAEs (intranasal rash and pruritis) that may have been attributed to intranasal 2% No-Bug cream or 4% No-Scrub sanitizing cloths were collected; participants in Groups 1 and 3 were not assessed for OAEs.
Source Vocabulary Name for Table Default	[Not specified]
Collection Approach for Table Default	Systematic Assessment

Issues With Reporting – Specific Events Assessed

Cluster Randomized Study Design Example

▼ Other (Not Including Serious) Adverse Events

Frequency Threshold for Reporting Other Adverse Events	0%

	Group 1: Standard Care	Group 2: Targeted Decolonization Plus Standard Care	Group 3: Enhanced Room Disinfection Plus Standard Care
	Affected / at Risk (%)	Affected / at Risk (%)	Affected / at Risk (%)
Total	0/0	22/39,456 (0.06%)	0/0
Skin and subcutaneous tissue disorders			
Intranasal rash †	0/0	7/39456 (0.02%)	0/0
Pruritus †	0/0	15/39456 (0.04%)	0/0

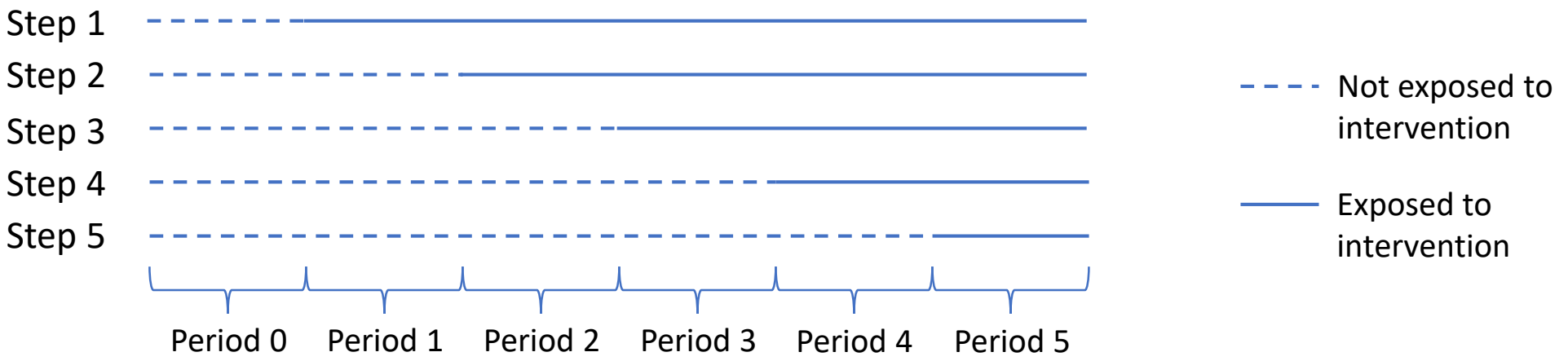
† Indicates events were collected by systematic assessment.

Zero at risk in groups that were not assessed

Issues With Reporting

3. How should the participant flow tables be represented for a stepped-wedge study design?

- Each arm should represent a unique experience to which a participant might be assigned. For a stepped-wedge trial, this means that each arm should reflect the transition from the pre-intervention to the intervention period.
- In the example below, each step would be an arm:



Issues With Reporting – Stepped Wedge Design

Arm/Group Title	Step 1	Step 2	Step 3	Step 4	Step 5
▼ Arm/Group Description	Participants in Step 1 received no intervention in the first study period (Period 0), but began receiving the intervention in the second period (Period 1) and remained on the intervention for the remainder of the study.	Participants in Step 2 received no intervention in the first two study periods (Periods 0 and 1), but began receiving the intervention in the third period (Period 2) and remained on the intervention for the remainder of the study.	Participants in Step 3 received no intervention in the first three study periods (Periods 0-2), but began receiving the intervention in the fourth period (Period 3) and remained on the intervention for the remainder of the study.	Participants in Step 4 received no intervention in the first four study periods (Periods 0-3), but began receiving the intervention in the fifth period (Period 4) and remained on the intervention for the remainder of the study.	Participants in Step 5 received no intervention in the first five study periods (Periods 0-4), but began receiving the intervention in the sixth period (Period 5) and remained on the intervention for the remainder of the study.

Period Title: **Period 0**

Type Units Assigned: Clinics	Number of participants	Number of units (Clinics)	Number of participants	Number of units (Clinics)	Number of participants	Number of units (Clinics)	Number of participants	Number of units (Clinics)	Number of participants	Number of units (Clinics)
Started	50	20	50	20	50	20	50	20	50	20
Received No Intervention	50	20	50	20	50	20	50	20	50	20
Received Intervention	0	0	0	0	0	0	0	0	0	0
Completed	50	20	50	20	50	20	50	20	50	20
Not Completed	0	0	0	0	0	0	0	0	0	0

Period Title: **Period 1**

Type Units Assigned: Clinics	Number of participants	Number of units (Clinics)	Number of participants	Number of units (Clinics)	Number of participants	Number of units (Clinics)	Number of participants	Number of units (Clinics)	Number of participants	Number of units (Clinics)
Started	50	20	50	20	50	20	50	20	50	20
Received No Intervention	0	0	50	20	50	20	50	20	50	20
Received Intervention	50	20	0	0	0	0	0	0	0	0
Completed	50	20	50	20	50	20	50	20	50	20
Not Completed	0	0	0	0	0	0	0	0	0	0

The Arm/Group Descriptions and Additional Milestones are used to indicate the timing of the intervention for each arm

Both numbers of participants and numbers of clusters are included for each arm

Periods 2-5

Thank you!

General Questions, Help With Records
register@clinicaltrials.gov

ClinicalTrials.gov Modernization Information
https://clinicaltrials.gov/ct2/about-site/modernization