The REDCap Advanced Randomization Module: A Trial Innovation Network Project to Support the Needs of Modern Trials

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TRIAL INNOVATION NETWORK

CTSA Clinical & Translational Science Awards Program

Conflict of Interest

Funding:

- National Heart Lung and Blood Institute (NHLBI)
- Department of Defense (DoD)
- Patient-Centered Outcomes Research Institute (PCORI)
- National Center for Advancing Translational Sciences (NCATS)

Conflicts of Interest:

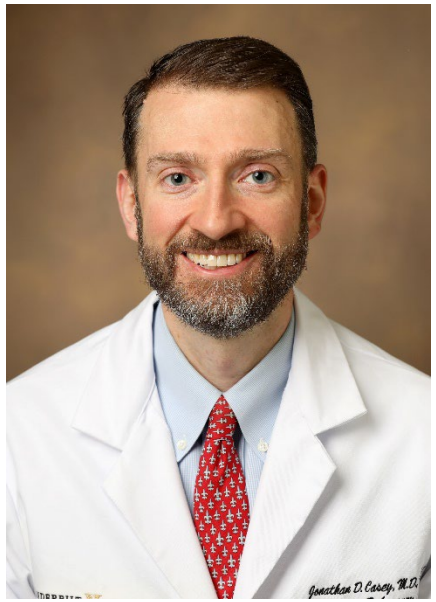
- Personal fees from Reprieve Cardiovascular, Inc

Agenda

1. Platform, Adaptive, Pragmatic and Decentralized Trials
   - What problems are they trying to solve?
   - Requirements of a randomization system to support advanced trial designs
2. Randomization in REDCap
   - Historical functionality
   - Design and release of the REDCap Advanced Randomization Module
3. Toughest question for clinical trial efficiency
   - How the Trial Innovation Network can help!

Disclaimer

Who am I?



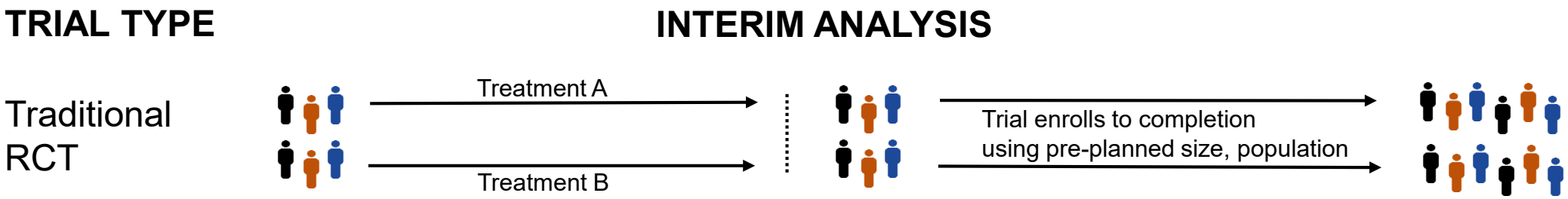
TRIAL INNOVATION NETWORK

PRAGMATIC CRITICAL CARE RESEARCH GROUP

Who am I not?

- Biostatistician
- Bioinformaticist
- REDCap Super User

Traditional Randomized Trials



- All trial procedures including eligibility criteria, group allocation, intervention, and sample size are specified before the trial and proceed **unchanged** throughout trial conduct

Challenges of Traditional Trials

- Expensive and take a long time
- Designed to answer only one question

- Rely on assumptions regarding baseline event rate/outcome distribution and effect size
- Commonly provide results that are uninformative (underpowered)

- May be affected by imbalances in key baseline characteristics
- Patients may have concerns with being randomized to placebo

- May not be available to many types of patients (poor generalizability)

Proposed Solutions

Example of Advanced Trials Designs

TRIAL TYPE

Needs of a Randomization System to Support Advanced Trial Designs

- Platform trials
  - Add/drop groups as questions are added or dropped from the platform
  - Multiple randomizations in same record (different domains or points in time)

- Sequential, Multiple Assignment, Randomized Trial (SMART) Designs
  - Tests “adaptive interventions” using defined decision rules for selection of the intervention at each stage
  - Multiple randomizations in same record at different stages of a patient’s clinical course

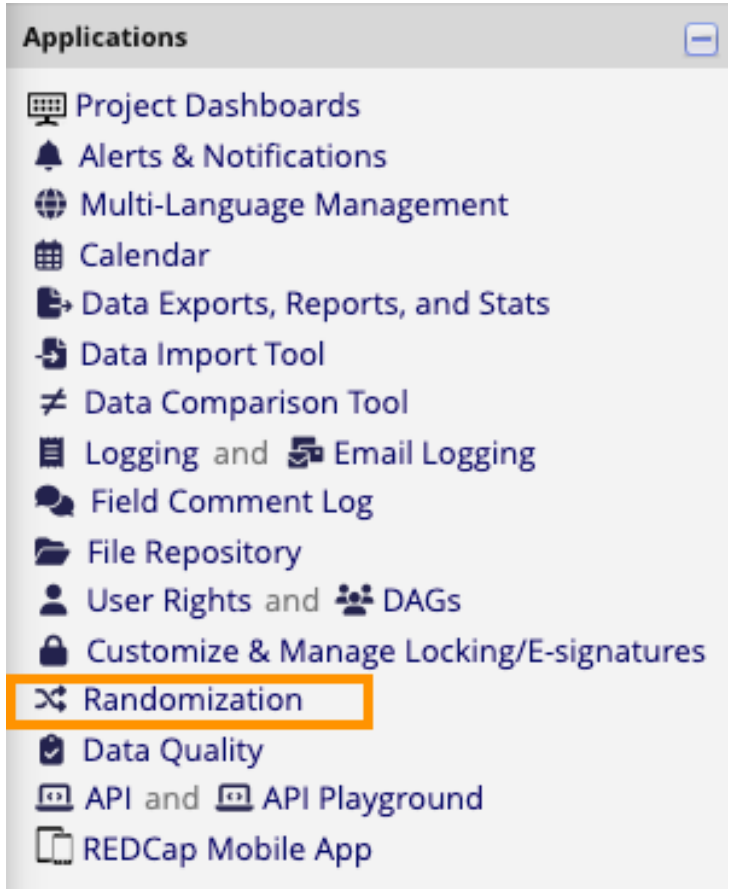
- Adaptive randomization
  - Ability to generate randomization sequence that changes allocation probabilities based on baseline characteristics of prior/current participants (covariate-adjusted randomization) or outcomes of prior participants (response-adaptive randomization)

- Pragmatic and Decentralized trials
  - Ability for randomization to be conducted without involvement of research personnel (e.g., randomization in back of ambulance or embedded in routine care in a rural clinic)

REDCap

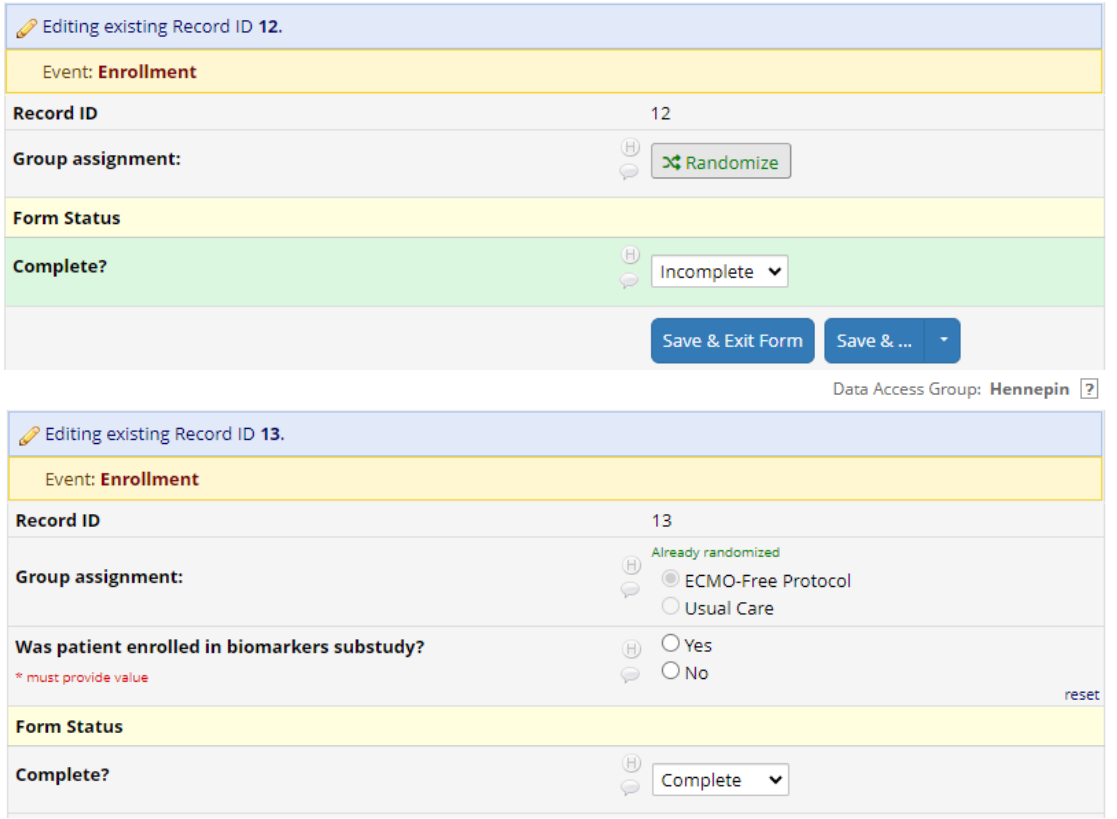
Research Electronic Data Capture

- Secure web platform for building and managing online databases, available at no cost to nonprofit, academic, and government organizations
- Created in 2004 at Vanderbilt University, supported by the NCATS CTSA program.
- One of the most commonly used platforms for clinical trials
  - 7,857 active partners in 160 countries.
  - 2,400,000 projects from over 3,700,000 users.
  - 46,400 journal articles cite REDCap.
- Has included an embedded tool for randomization since 2012



Prior REDCap Randomization Tool

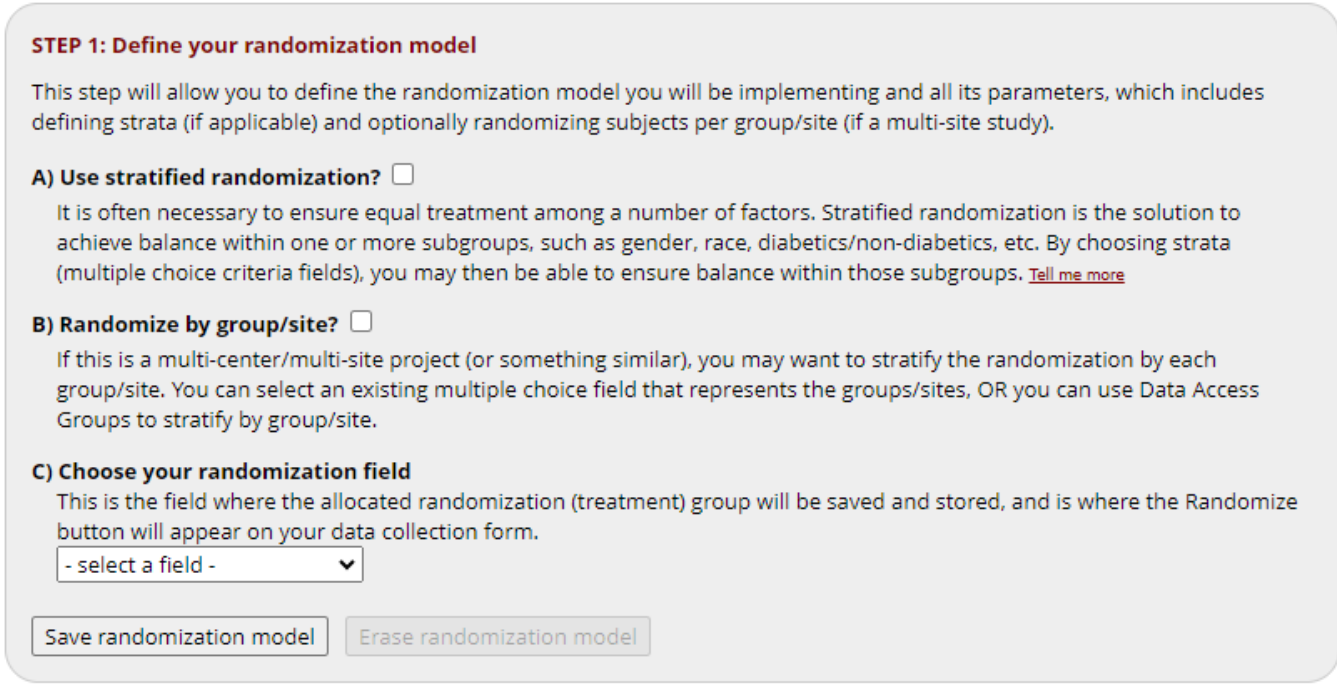
- User-friendly tool to embed randomization into data collection instrument
- Allows single randomization for each study record
  - Randomization is time-stamped and linked to user performing randomization (meta-data)



11/21/2023 9:03am	elias_pratt	Update record 129285-3 (Randomization)	randomization_complete = '2'

Capability of Prior REDCap Tool

- Existing REDCap tool had features commonly applied in traditional RCTs
  - Stratification by site
  - Use of additional stratifying variables to minimize differences in key variables (e.g., age, sex)



Capability Gaps with Prior REDCap Tool

- Once set, randomization schedule is fixed and cannot be modified
  - Unable to add/drop groups or change allocation ratio
- Only allows one randomization per study record
  - Unable to randomize into multiple domains or at multiple points in time
- Unable to embed models that use baseline characteristic or outcomes of prior participations to generate randomization probabilities
- Randomization can only be conducted by study personnel with access to database (cannot be embedded in survey)
- Requires additional steps to blind user to group allocation

Example Trial

- Placebo-controlled dose-finding trial of novel antiarrhythmic following prolonged cardiac arrest.
  1. Randomize in the ambulance
  2. Blind clinicians using numbered identical med packs
  3. Drop worst performing arm when transitioning from Phase 2 to Phase 3
  4. Use adaptive randomization to balance baseline covariates
  5. Bayesian sequential design to continue trial until definitive evidence of efficacy, harm, futility

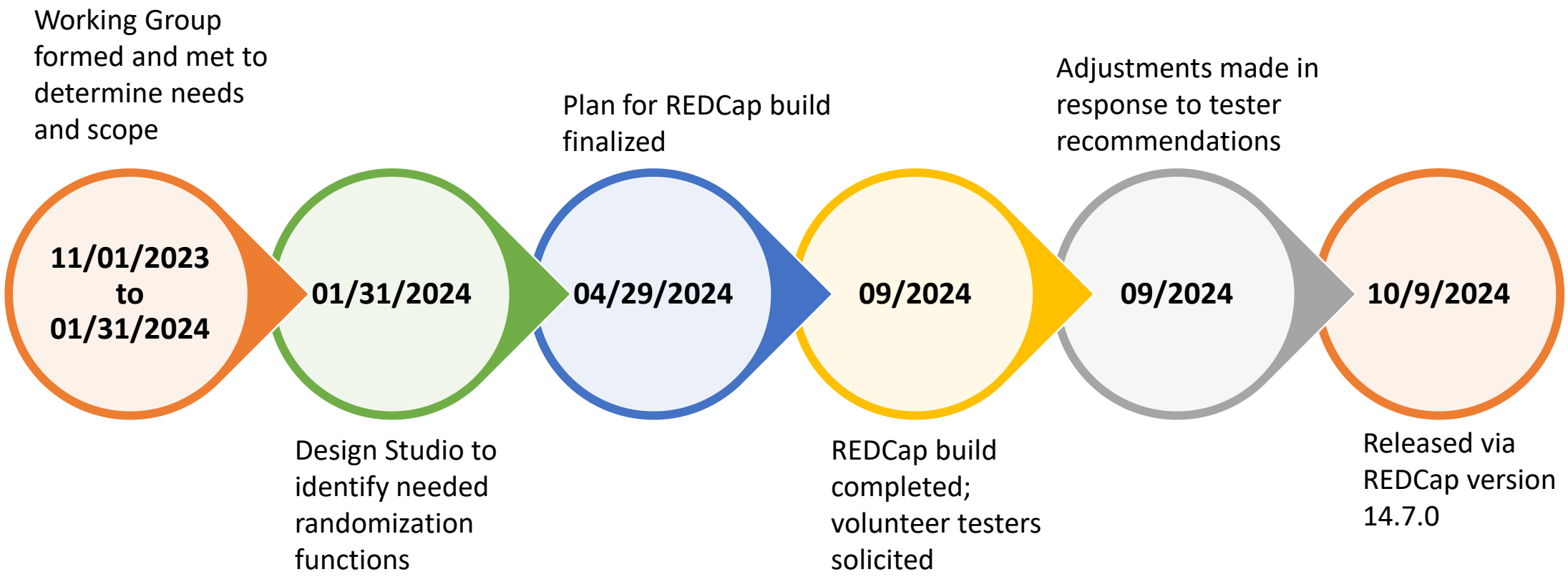
Examples of User Workarounds

- Users were copying databases to “unlock” the randomization tool to allow a new randomization table to be uploaded
  - Creating multiple projects and requiring updates to user access (weekly) and losing meta-data

- Custom-building randomization tools that provided needed functionality but required significant effort and coding expertise (e.g., manually recreating the randomize button) and lacked embedded data protections (meta-data for randomization)

- Many users felt forced to use separate cloud-based randomization tools

Development of the REDCap Advanced Randomization Module: A Trial Innovation Network Project



Advanced Randomization Module Team

Paul Harris
REDCap Creator

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Clinical Researcher

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Biostatistician

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Expert REDCap Developer

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Statistician and Researcher

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Project Manager

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Lead REDCap Developer

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REDCap Product Manager

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VUMC TIC Manager

Luke Rasmussen
Clinical Researcher

Northwestern University

Vanderbilt University Medical Center

New Functionality in Advanced Randomization Module

1. Multiple randomizations
2. Improved support for blinding
3. Additional meta-data for randomization
4. Support for pragmatic and decentralized Trials
5. New administrator-level allocation management features
6. Hook/extension functions for external modules
7. Integration with non-REDCap systems
8. Randomization dashboard

1 Multiple Randomizations

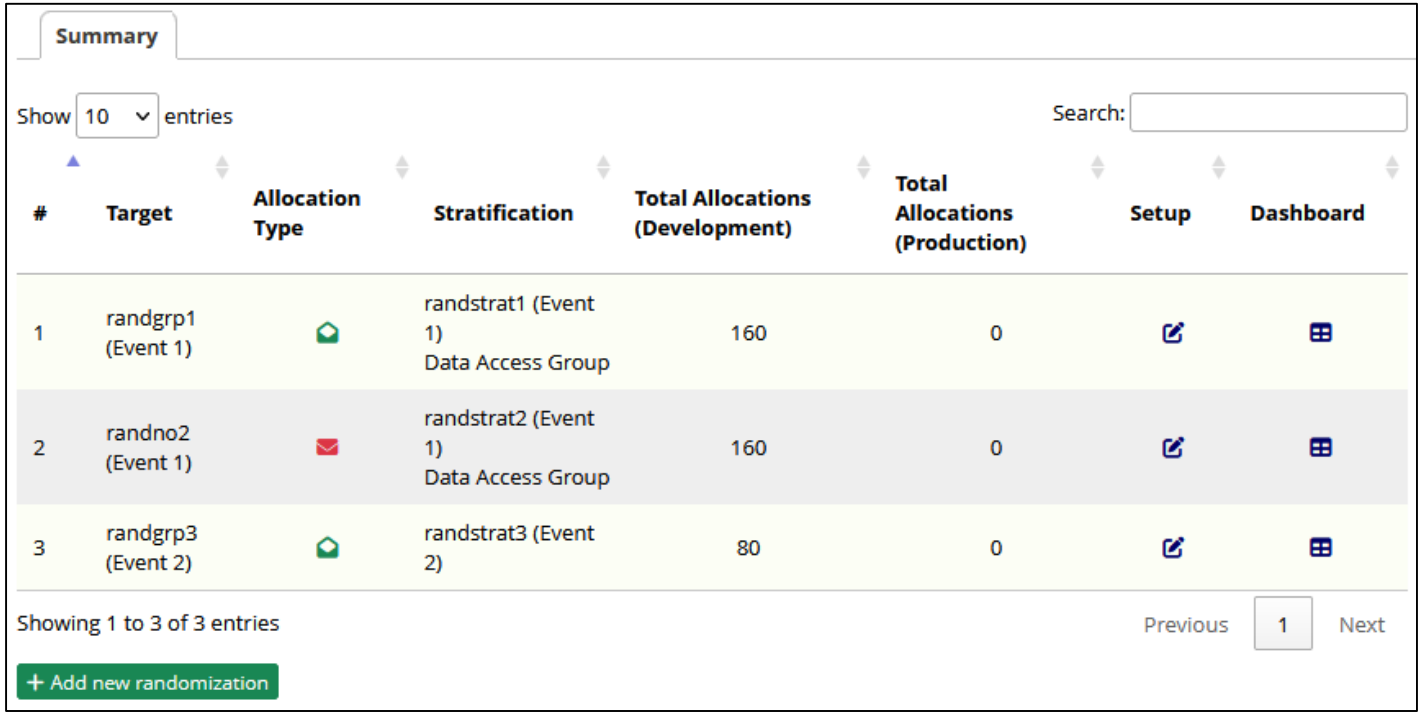
Rationale/Need:

- Platform trials, adaptive trials and Sequential, Multiple Assignment, Randomized Trial (SMART) Trials may require:
  - Randomizing patients in multiple domains and/or at multiple points in time.
  - Updating future randomization tables
- Desire to maintain the initial randomization code and its meta-data for data integrity
- Seamless integration and backward compatibility of existing tool

1 Multiple Randomizations

Features:

- Ability to create multiple randomizations tables to:
  - Allow multiple randomizations in the same patient
  - Replaced (hide) initial randomization sequence with an updated randomization sequence
- Unchanged user experience for projects with one randomization.



2 Blinding

Rationale/Need:

- Prior REDCap tool did not have built-in capability for blinding
  - By default, personnel performing randomization received group assignment
  - Blinding was possible using additional REDCap features (e.g., hidden fields and branching logic) but unintentional unblinding was possible

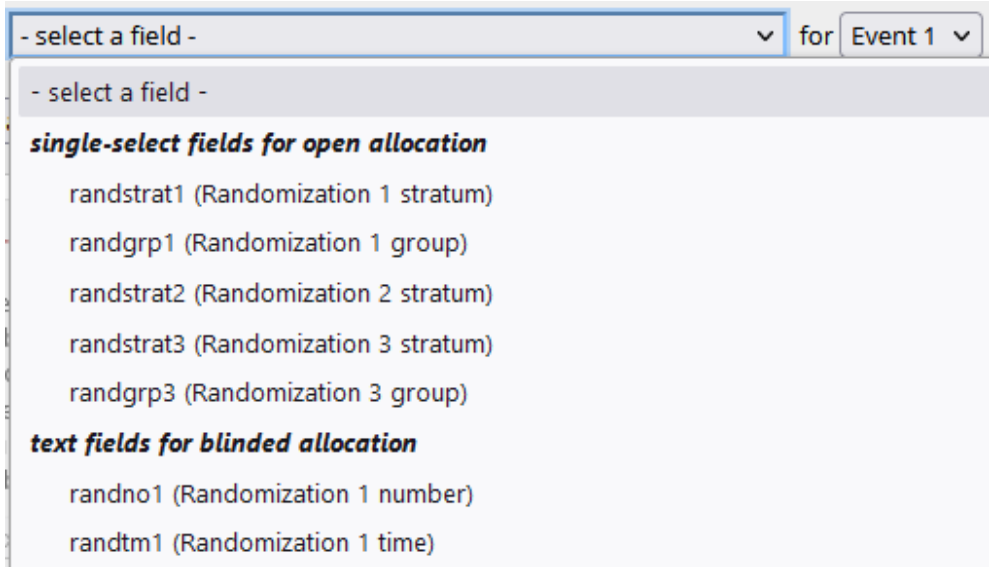
- Prior REDCap tool lacked the ability to link individual randomization to sequence on the master list (ie, randomization numbers)
  - Hard to track/report randomization (e.g., during an audit)
  - Hard to link randomization sequence to individual medication packages (weakening chain of custody measures)

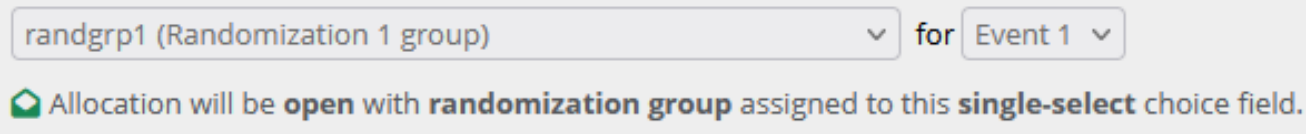
2 Blinding in Advanced Randomization Module

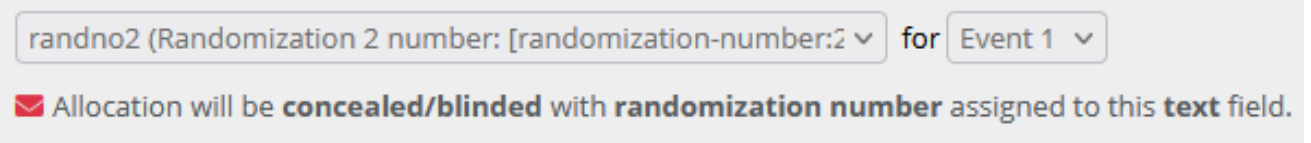
Features:

- Randomization can reveal:
  - Group allocation; or
  - Randomization number

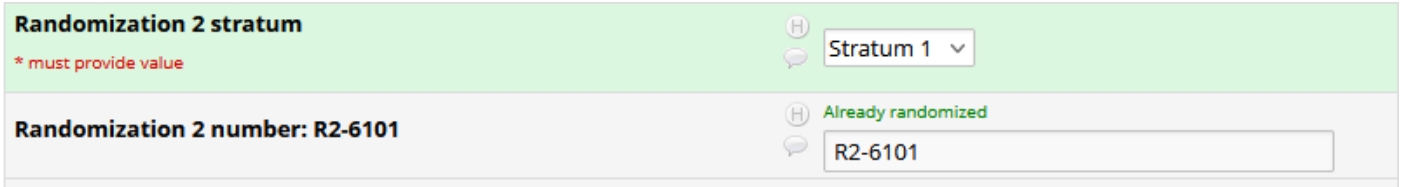
- When using randomization number (blinding), unblinded personnel can match to a medication pack or translate to group assignment using:
  - Look-up table
  - Separate project (piping)







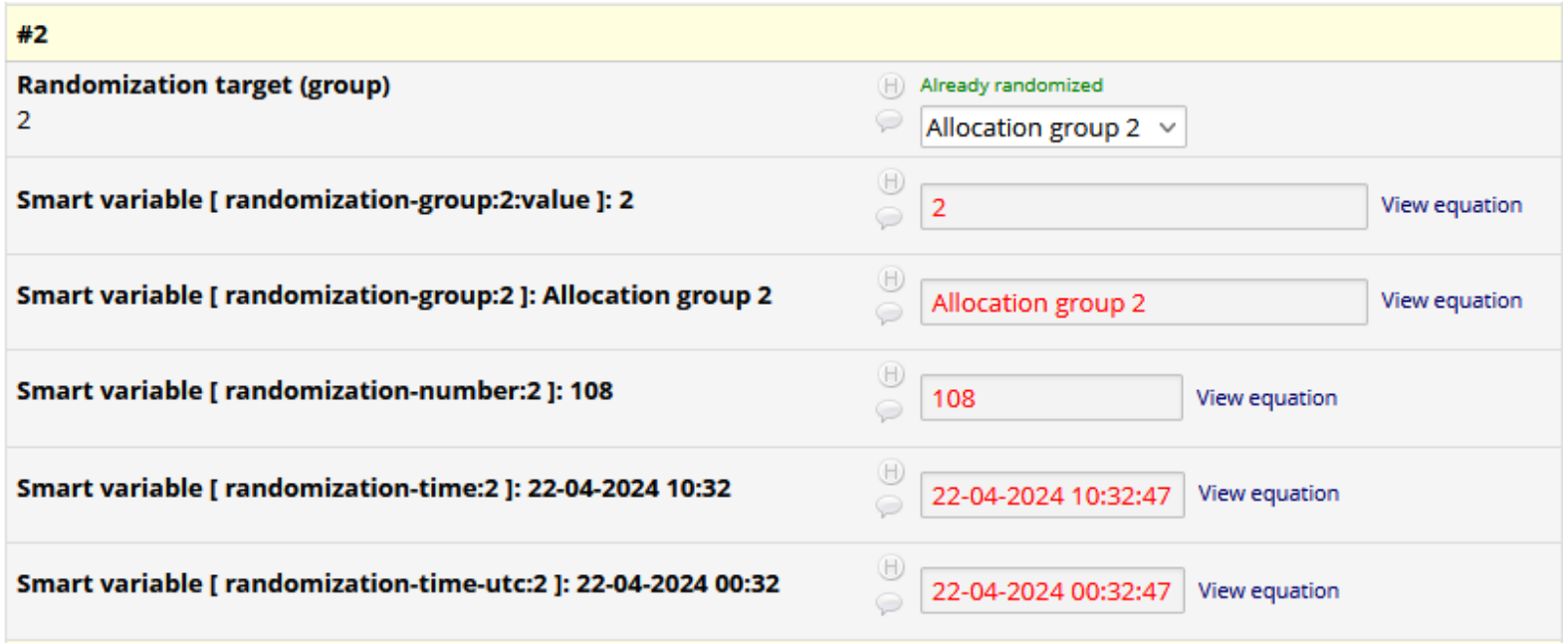
	A	B	C	D
1	redcap_randomization_number	redcap_randomization_group	randstrat2	redcap_data_access_group
2	R2-6101	Blinded Group 1	1	6
3	R2-6102	Blinded Group 2	1	6
4	R2-6103	Blinded Group 1	1	6
5	R2-6104	Blinded Group 2	1	6
6	R2-6105	Blinded Group 1	1	6



3 Meta-Data in Advanced Randomization Module

Rationale/Need:

- Meta-data (information about other data) for randomization can be helpful for tracking/audits
- Previously available through built-in logging function but not be included in the trial dataset
- New SMART variables can be used to automatically include metadata on randomization in trial dataset



- Smart variables
  - [rand-group], [rand-number], [rand-time], [rand-time-utc]

4 Support for Pragmatic and Decentralized Trials

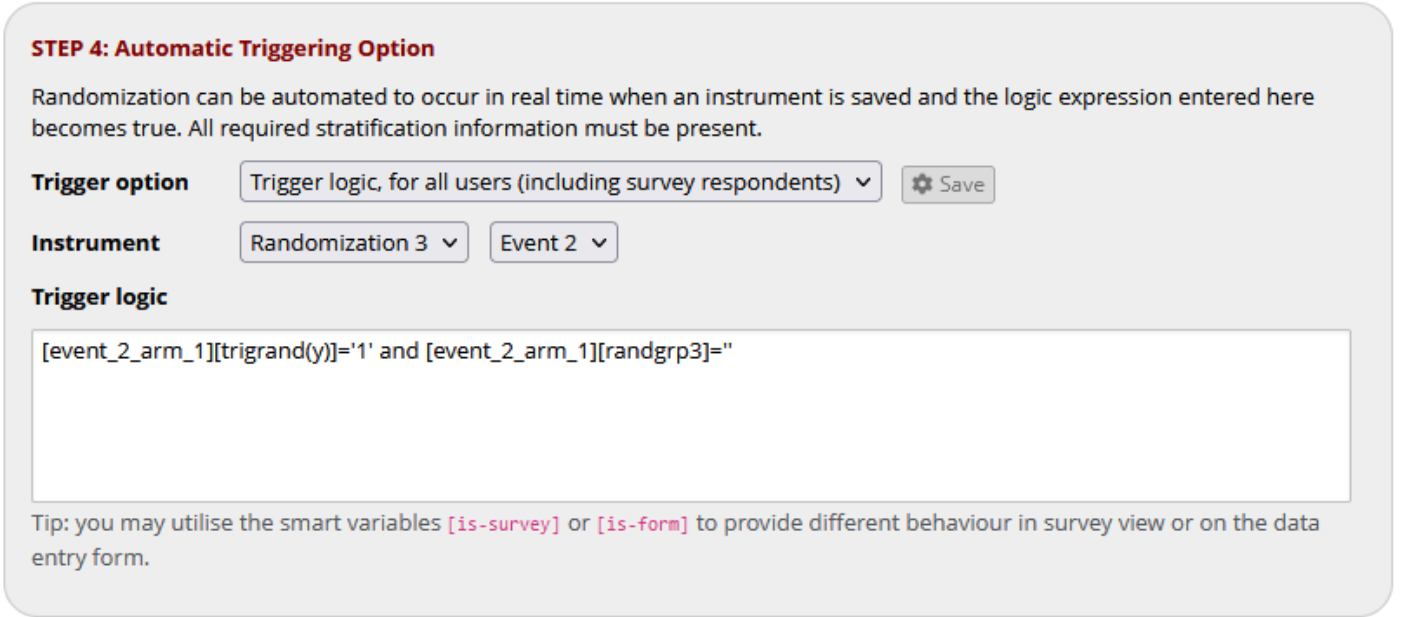
Rationale/Need:

- Some decentralized and pragmatic trials may have non-research personnel performing eligibility assessments, enrollment, and randomization (e.g., randomization by an EMS provider in the back of an ambulance)
- Previously, randomization could only be performed by users with access to the study database and similar limitations exist with most, alternative randomization platforms
- Currently, many pragmatic and decentralized trials rely on less robust randomization procedures
  - Physical randomization procedures (e.g., opaque envelopes)
  - Cluster-randomization

4 Support for Pragmatic and Decentralized Trials

Features:

- Automatically performs a randomization on form save when logic condition is true
- Allows randomization to be embedded in a survey that can be accessed with a link (or QR code)
- Options:
  - ➢ Off: Manually click “Randomize” button to randomize
  - ➢ Trigger for users with “Randomize” permission only
  - ➢ Trigger for all users – including as a survey



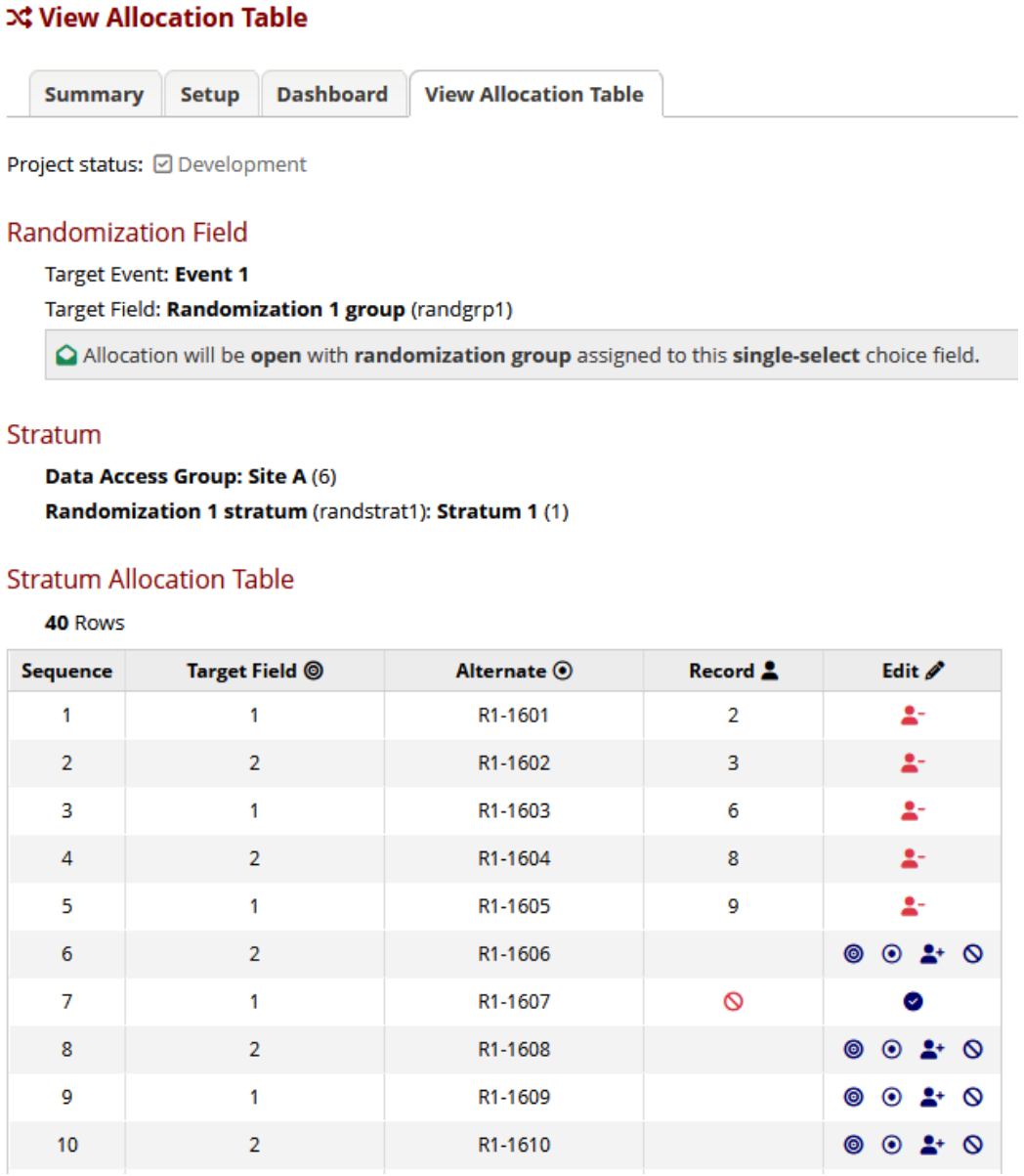
5 Administrator Editing Tools

Rationale/Need:

- Rare circumstances arise in which an administrator may need to add or alter a randomization allocation (e.g. randomization during downtime)

Features:

- Administrator access from Dashboard for (rare) actions:
  - ➢ Manual randomization, remove a randomization, make list entry unavailable/ available
- All actions are logged (user, date/time, change made) and mandate a comment explaining the reason for the modification



6 Hook/extension functions for external modules

Rationale/Need:

- Adaptive randomization, changing allocation probabilities based on baseline characteristics of prior/current participants requires:
  - Accessing data from other records within the database
  - Running analytic models to calculate probabilities for future randomizations based on study-specific goals (covariate-adjusted randomization, response-adaptive randomization)

- No randomization tool could support the needs of all current and approaches to adaptive randomization, but some approaches are reusable across trials.

6 Hook/extension functions for external modules

- The External Module Framework provides various "hook functions" – specific points in REDCap's code into which module developers may inject their own custom functions
- Integration of external module into the randomization module allows:
  - Increased flexibility for users to design and share modules built for specific types of adaptive randomization
  - Maintain the protections of the REDCap tool (meta-data)
  - Simplify the development process (no longer required to rebuild functionalities such as the “Randomize” button)

redcap_randomize_record (REDCap >= 17.?.?)

`redcap_randomize_record` — Allows custom actions to be performed prior to the randomization of a record e.g. to override the default randomization allocation.

Description

```
void redcap_randomize_record ( int $project_id, int $randomization_id, string $record, array $field_values, int $group_id )
```

It is expected that only one external module implementing this hook will be enabled in a single project. A warning will be generated if multiple external modules return results from this hook.

Location of Execution

The function is executed immediately prior to lookup and assignment of the next available entry in the randomization allocation table. This lookup and allocation is skipped if all redcap_randomize_record hooks return false.

README GPL-3.0 license

REDCap External Module: Extended Randomisation

Luke Stevens, Murdoch Children's Research Institute https://www.mcri.edu.au/

https://github.com/lsgs/redcap-extended-randomisation2

Summary

REDCap external module for dynamic randomisation (biased coin minimisation) utilising the new `redcap_randomize_record()` hook.

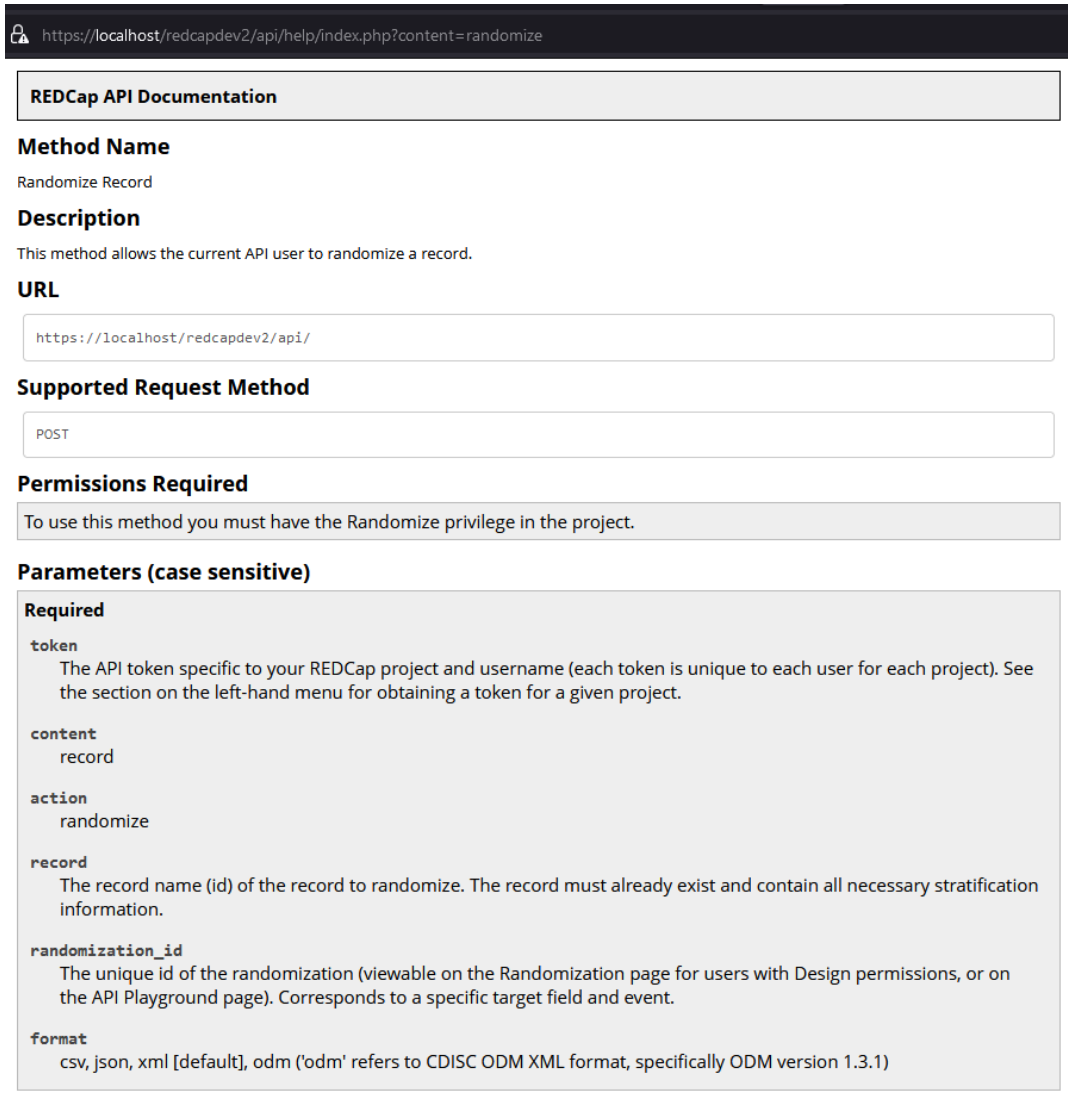
7 Integration with non-REDCap systems

Rationale/Need:

- Some projects may have special project-specific approaches to adaptive randomization that can only be built on an external platform/server.

Features:

- Advanced REDCap randomization module allows randomization to pull group allocation from a platform outside of REDCap using an API
- Maintains user-friendly REDCap interface and REDCap protections (e.g., meta-data)
- Can also be used to pull randomizations from REDCap into other systems that lack advanced features (e.g., electronic health records).



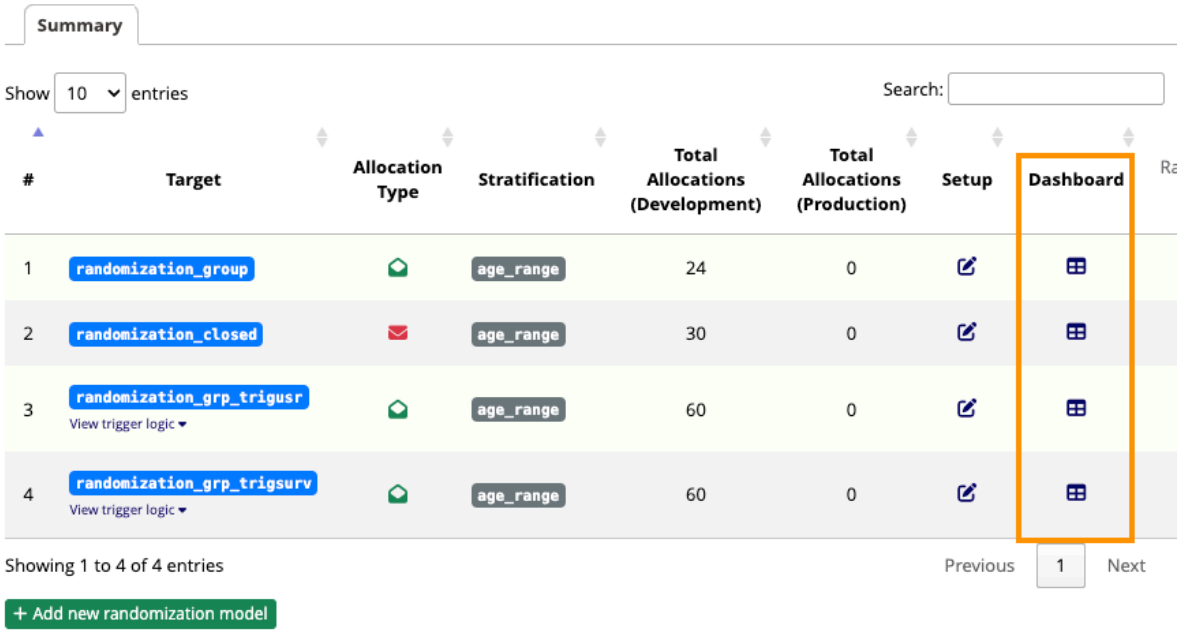
8 Randomization Dashboard

Rationale/Need:

- Previously, no method of tracking the number of randomizations used
- Could exhaust available randomizations

Features:

- Randomization dashboard provides information on the number of allocations used and reaming to users with the appropriate privileges
- Can show information about specific allocations (for unblinded trials) or limit data to strata (for blinded trials).



Used	Not Used	Allocated records	Age Range age_range
0	5		18-24 (18)
1	4	1	25-34 (25)
0	5		35-44 (35)
0	5		45-54 (45)
0	5		55-64 (55)
1	4	2	65+ (65)

Example Trial

- Placebo-controlled dose-finding trial of novel antiarrhythmic following prolonged cardiac arrest.
  1. Randomize in the ambulance
  2. Blind clinicians using numbered identical med packs
  3. Drop worst performing arm when transitioning from Phase 2 to Phase 3
  4. Use an external module for adaptive randomization to balance baseline covariates
  5. Bayesian sequential design to continue trial until definitive evidence of efficacy, harm, futility

How do I learn how to use these new features?

- REDCap home page (www.redcap.vumc.org)
  - Step-by-step guide that can be accessed via the 'Visit the Help Resources page' link
  - Video tutorial accessed from the 'Training Resources' link."

- Resources made by the REDCap user base
  - Seattle Children's: https://redcap.seattlechildrens.org/surveys/?s=3oa2yzEgQrpXp4wy#privileges

Next Steps

1. Methods/dissemination manuscript under review
2. Incorporation of the randomization functionality into REDCap's 21CFR Part 11 Validation framework
3. Exploring methods to support randomization within the EHR for pragmatic, EHR-embedded trials

Toughest Question for Clinical Trial Efficiency?

-

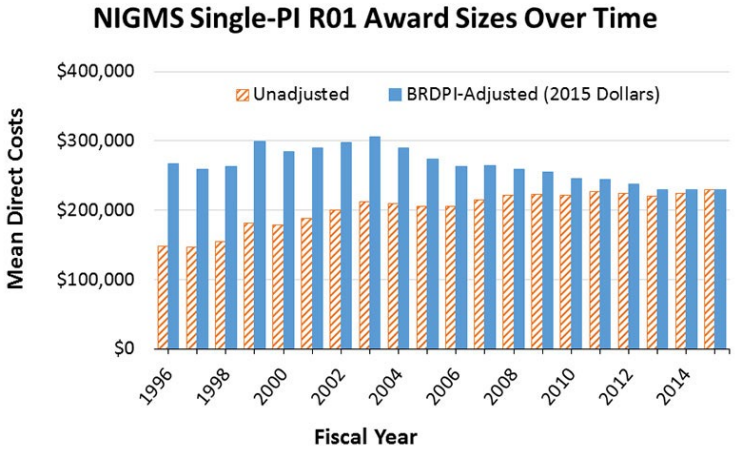
What is “efficiency” in a clinical trial?

$$\text{Efficiency} = \frac{\text{Output}}{\text{Input}} = \frac{\text{Evidence to inform patient care}}{\text{Money, time, \& effort}}$$

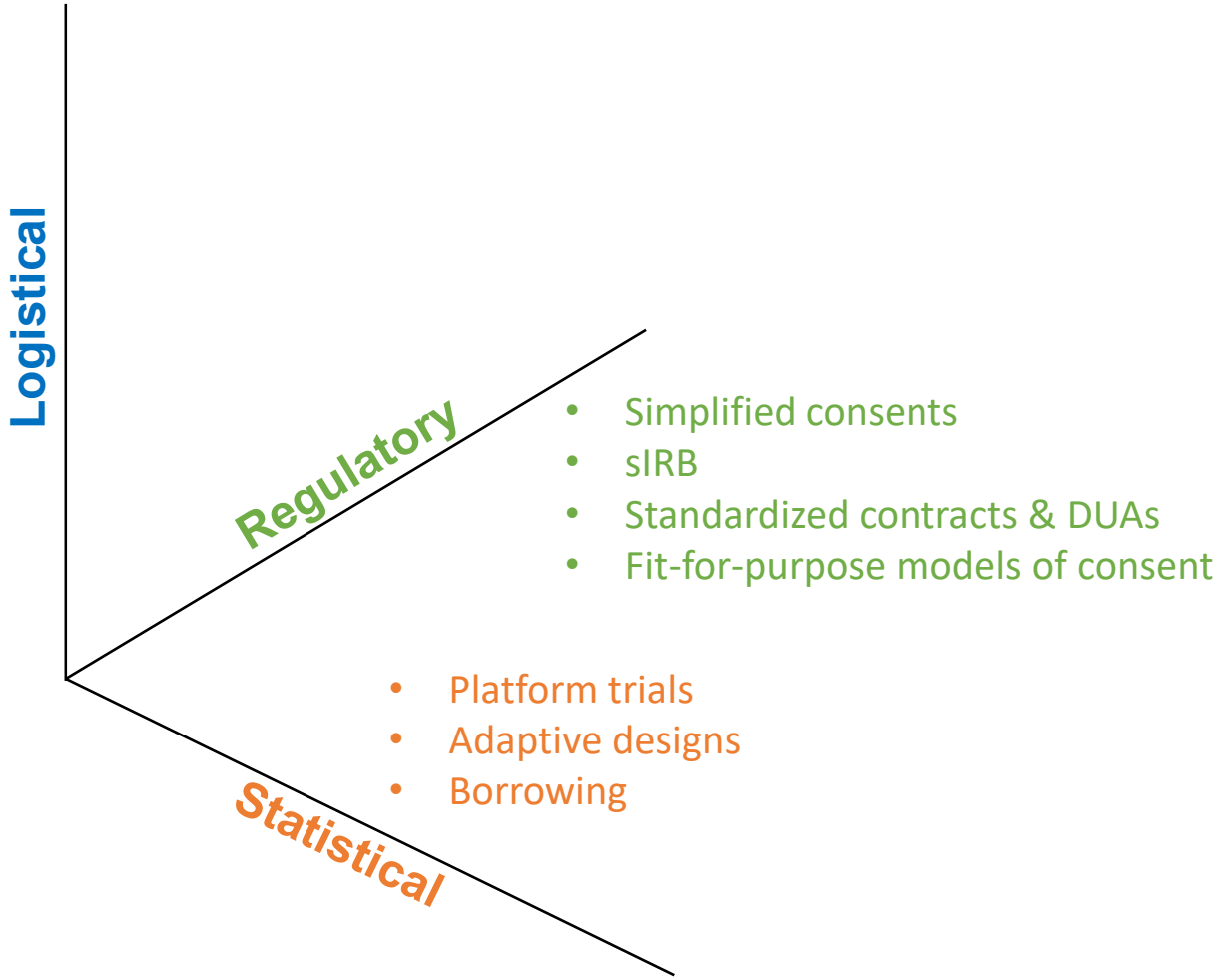
Why must clinical trials be efficient?

- Resources for clinical trials are limited

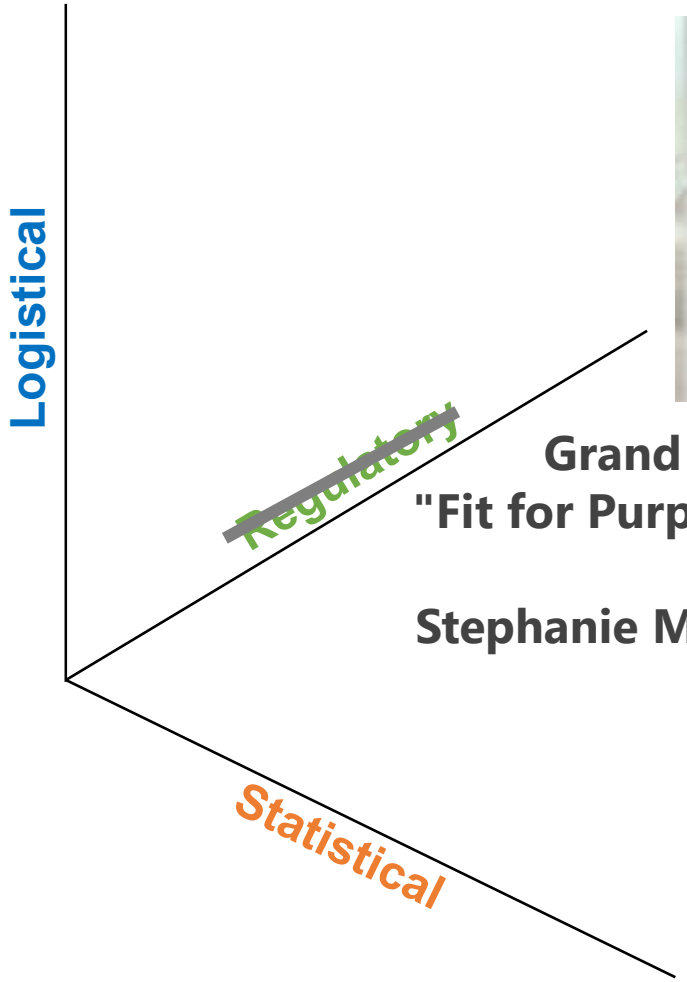
1. Personnel
   - Coordinating Centers, Trialists, Investigators, Coordinators, Statisticians, Patient and Community Partners
2. Funding



In what ways can a clinical trial be more efficient?

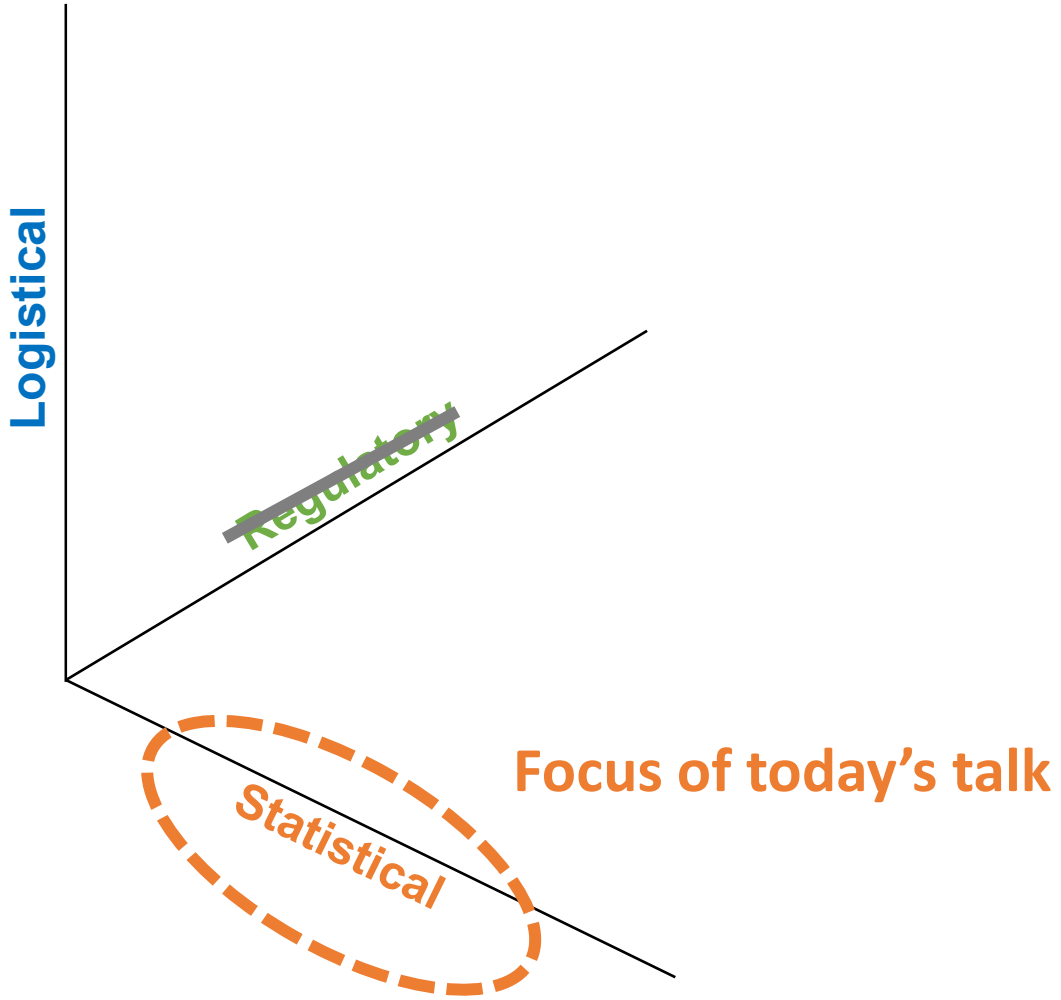


In what ways can a clinical trial be more efficient?

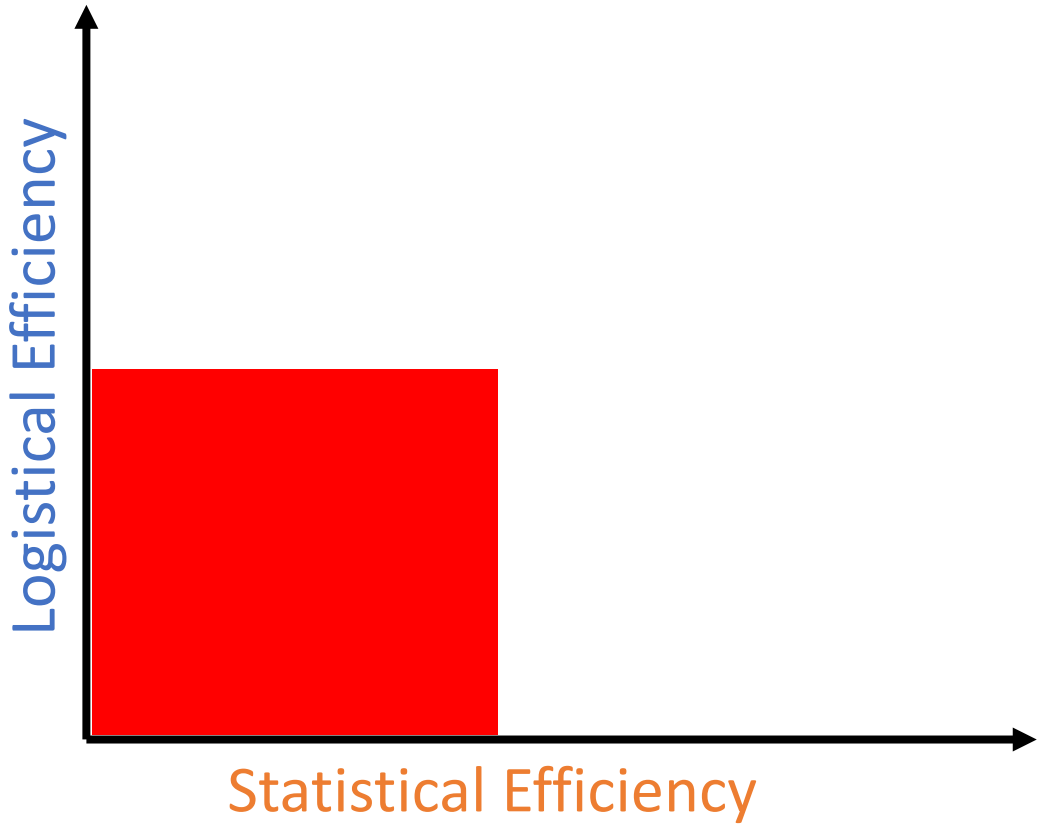


Grand Rounds Rethinking Clinical Trials:
"Fit for Purpose: Improving the Ethical Oversight of Pragmatic Clinical Trials."
Stephanie Morain, PhD, MPH, Nancy Kass, ScD, and Ruth Faden, PhD, MPH

In what ways can a clinical trial be more efficient?

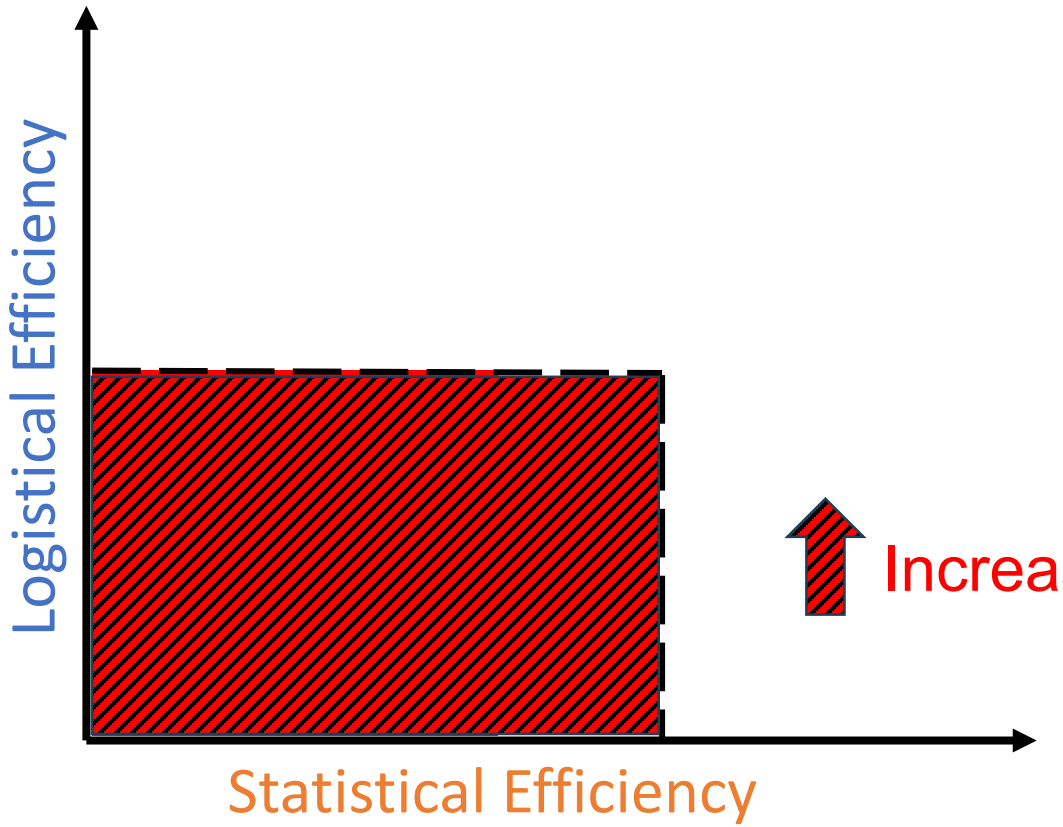


Trial Efficiency



Information learned = area under curve

Trial Efficiency

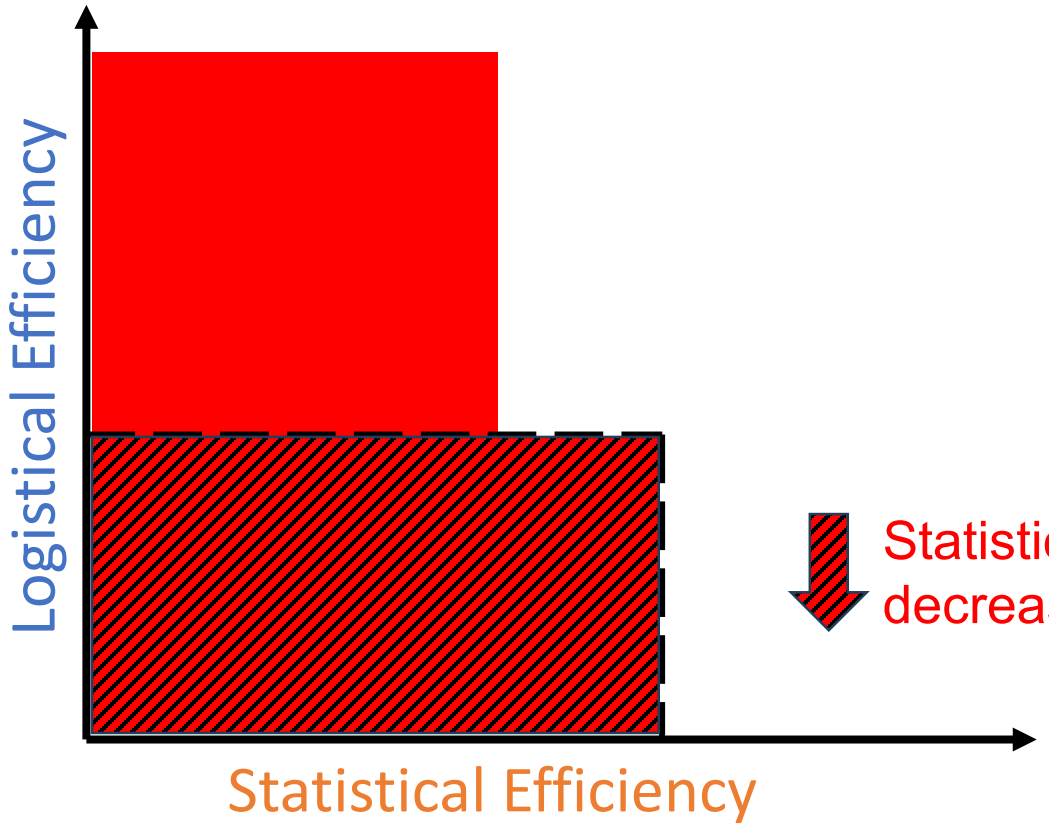


- Study: 100-patient, phase 1 trial of a novel infusion for treatment of hypotension, which is planned to enroll at 30 sites

Increased overall efficiency by 25%

Information learned = area under curve

Trial Efficiency

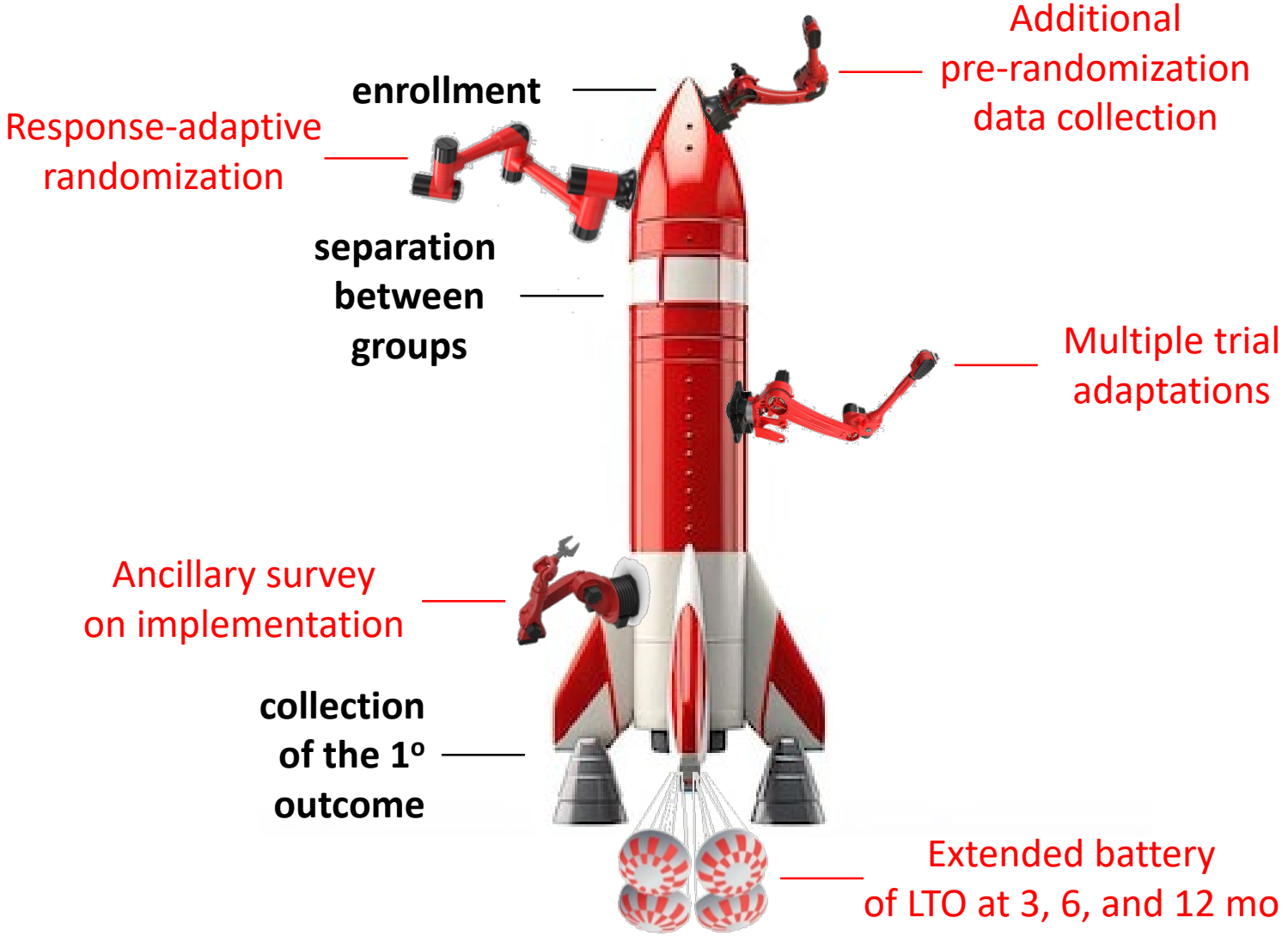


- Study: 2,364-patient, comparative effectiveness trial of sedative medication during emergency tracheal intubation at 6 sites.
- Design feature: Use of adaptive randomization to balance baseline covariates

Statistical efficiency increased but overall efficiency decreased

Information learned = area under curve

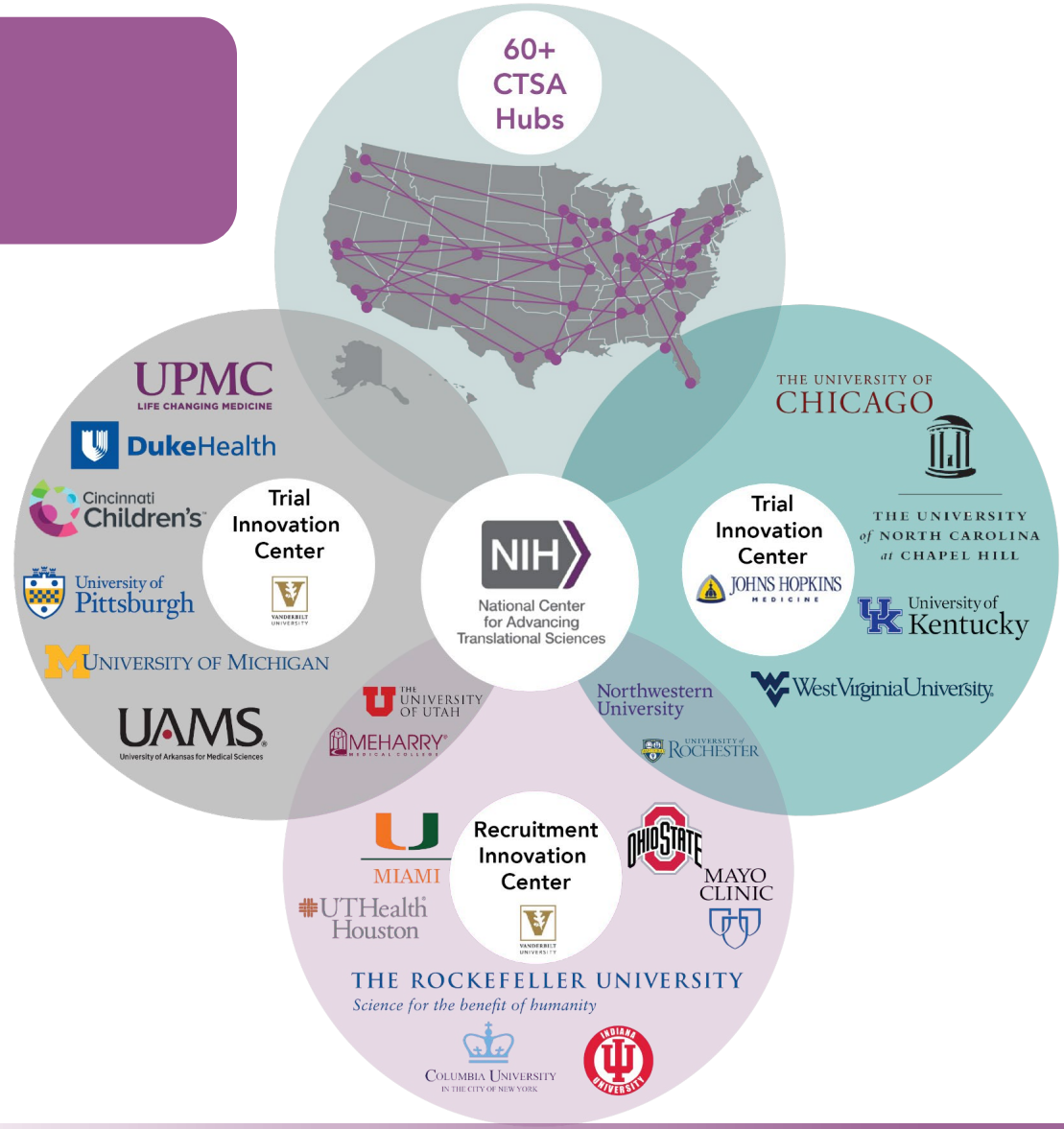
Ensuring Desing is Fit-for-Purpose



Trial Innovation Network (TIN)

TIN is an NCATS funded collaborative initiative within the CTSA Program.

- Seeking to innovatively address critical roadblocks in **multi-site clinical research**
- Developing, testing, and supporting **innovative operational and recruitment tools**.
- Offering **cost-free, structured scientific consultations** with clinical trial experts in various diseases across all stages of the trial process.



TRIAL **INNOVATION** NETWORK

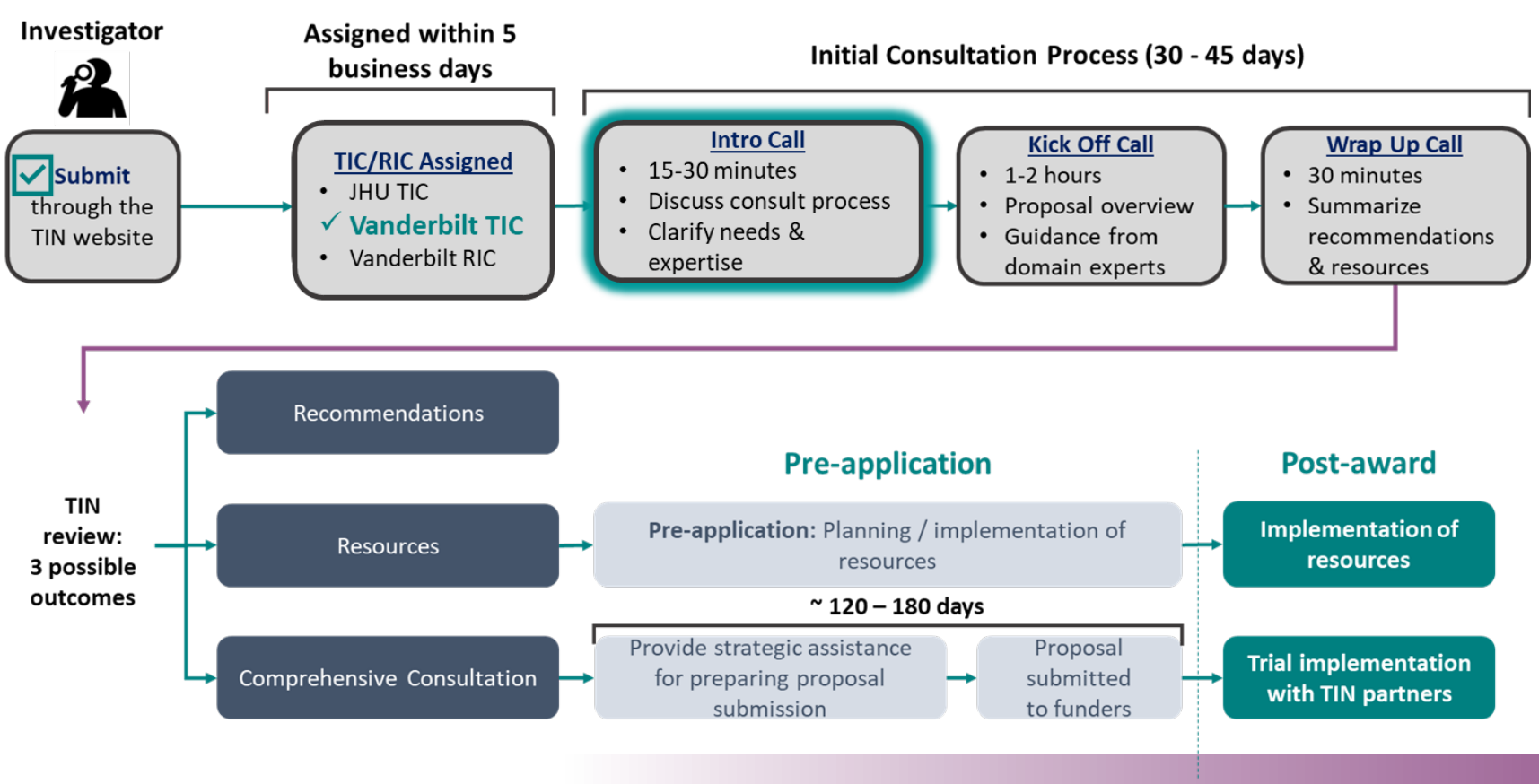
CTSA Clinical & Translational Science Awards Program

Requesting Help from the Trial Innovation Center

No Cost Scientific Consultations

The Trial Innovation Network offers investigators the opportunity to request consultations and resources for multicenter clinical trials and studies.

Proposal Process (scan)



TRIAL INNOVATION NETWORK

CTSA Clinical & Translational Science Awards Program

TIN Consultations & Resources

Investigators can request consultation and resources for multi-center clinical trials across disciplines and diseases.

453	**Initial Consultation**	All proposals submitted to the TIN portal are provided with an initial consultation
230	**Resources**	Individual studies approved for use of one or more TIN resource(s)
89	**Comprehensive Consultation**	Investigator and TIN work together to develop and submit a proposal
35	**Trial Implementation**	The TIN serves as the trial data or clinical coordinating center

TRIAL INNOVATION NETWORK

CTSA Clinical & Translational Science Awards Program

Collaborate with TIN

Since 2016:

431 completed consultations

Proposals covered
77 therapeutic areas

Proposals submitted to
21 NIH I/Cs

Scan to submit a proposal for a FREE scientific consultation.

TRIAL **INNOVATION** NETWORK

63 (96 %)

Number (%) of CTSA Submitted Proposals

34 %

Submissions funded at time of request

INVESTIGATOR ROLES	
PROFESSOR	55%
ASSOCIATE PROFESSOR	26%
ASSISTANT PROFESSOR	16%
INSTRUCTOR	2%
POST-DOC FELLOW	0.4%

*44% Mid- and Early-Career Roles, incl.

Top 10 Therapeutic Areas N=77

Cardiovascular Diseases	13%
Neurology	8%
Infectious Diseases	7%
Pediatric Disciplines	6%
Pulmonary Diseases	5%
Oncology	4%
Trauma	3%
Behavior Medicine (clinical)	2%
Gastroenterology	2%
Diabetes	2%

U24TR004437 (Vanderbilt University Medical Center)
U24TR004440 (Johns Hopkins University School of Medicine)
U24TR004432 (Vanderbilt University Medical Center)

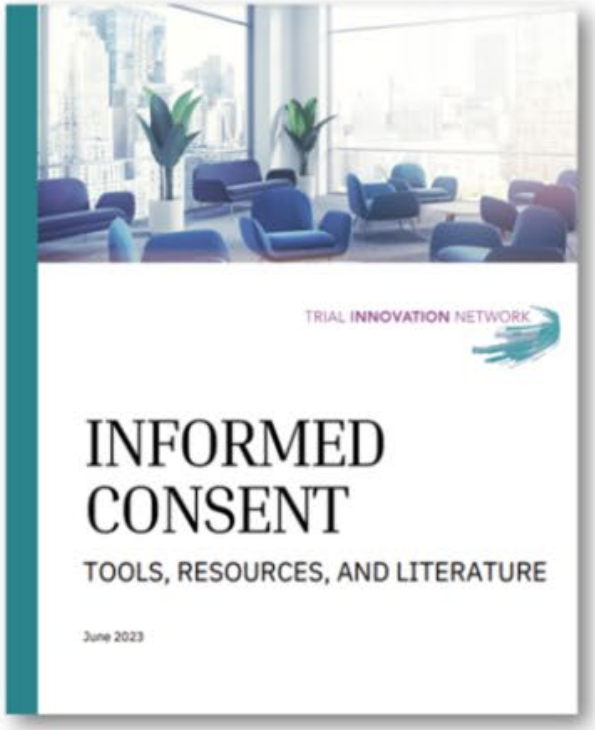
CTSA Clinical & Translational Science Awards Program

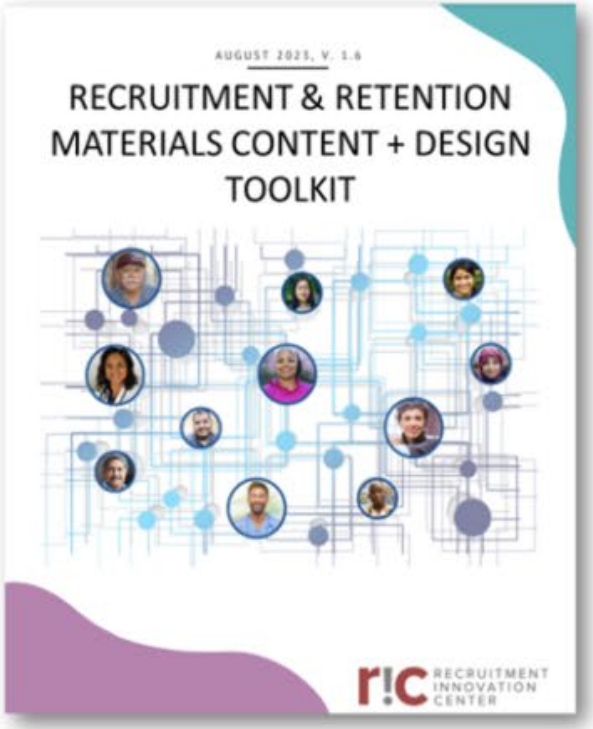
TIN Toolbox

TRIAL INNOVATION NETWORK

Dozens of evidence-informed resources and tools…

Examples:





…all FREE to the research community

Questions?

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