Randomization Design for a Double-Blinded Investigator Initiated Trial

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Description of the Problem

Underlying problems that arise during screening and randomization of potential patients in a research study can vary from system to system. Randomization processes typically include collecting screening data, answering selected stratification questions, then randomizing subjects to their appropriate cohort using a sponsor funded system.

For investigator initiated trials (IIT), it is crucial to find ways to ensure protocol compliance and minimize preventable errors. One way to do this is by limiting site staff from having control over enrolling patients to their appropriate cohort without oversight. Enrolling patients to the incorrect cohort and randomizing them to the incorrect treatment can result in the need for additional time, effort and resources that are not readily available for IITs.

In this case, the ADAM Trial is conducted at multiple sites. As a result it was important to develop a strictly regulated process and design a unique, double-blinded randomization schema without the use of funding from pharmaceutical companies nor the use of IWRS systems.

Objectives

- Full randomization oversight by investigator-sponsor.
- Ensure randomization remains double-blinded.
- Minimize randomization and cohort assignment errors.
- Successfully randomize and enroll a total of 100 subjects at 15 different sites.

Best Practice

To implement a randomization process that provides strict investigator-sponsor oversight and reduce potential errors in a double-blinded investigator initiated clinical trial.

Acknowledgements

ADAM Trial Team:
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Samantha Kiriluk, Vivian Nguyen,
Aubrey Poisson, Ted Gooley

Methods

The team created 3 versions of the randomization spreadsheet. The spreadsheet consists of the following unblinded and blinded columns:

- Cohort: Lists over 100 possible assignments for each of the 4 cohorts (cohorts are assigned based on protocol specified stratification variables).
- Verification Code: A randomly generated unique list that is used as part of the randomization process.
- Treatment Code: Another set of randomly generated unique list that is used as part of the randomization process.
- Treatment: To ensure a more secure process, the treatment column was filled with the Treatment Code to prevent accidental emails of treatment assignment to blinded personnel.
- Order: A set of numbers required by Medrio for the system to randomly select an enrollment spot.
- Subject ID: Site # - Subject # - Subject initials (i.e. 01-001-AAA)
- Treatment Assignment: Randomly ordered list of study drug and placebo treatment options.

Medrio, a data capturing system that provides tools for creating CRF pages and randomizing patients to a study treatment was utilized in the following ways:

- Creating a customized randomization CRF page.
- Set up of a randomization confirmation email that is sent to investigator-sponsor, appropriate pharmacy and study staff.
- Un-blinded pharmacists receive the email to match the provided codes and cohort with the unblinded spreadsheet to a treatment assignment.

Outcomes

- Modified Medrio's randomization tool by adding an extra layer of protection to ensure the trial remains double-blinded.
- Activated the ADAM Trial at 5 different sites. Successfully enrolled and randomized 6 patients with no errors.
- Cohort assignment performed only by investigator-sponsor to track the number of subjects enrolled in each of the different cohorts.
- Randomization email created consistent and efficient messaging to multi-site staff and pharmacists with accurate treatment codes and cohort number.

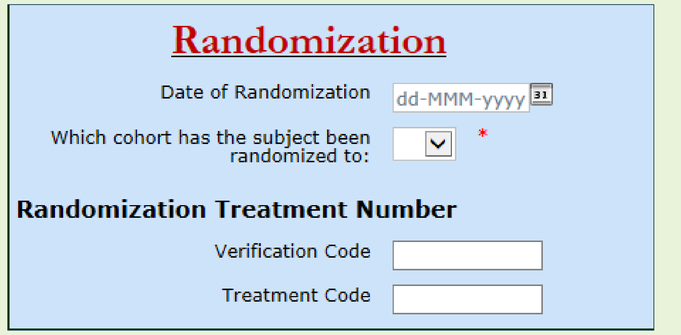
EXAMPLE 1: Blinded investigator-sponsor spreadsheet

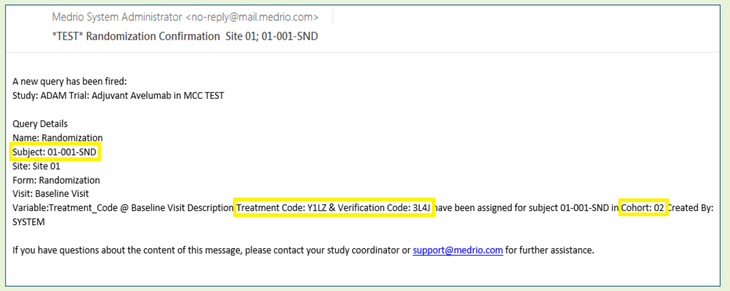
	A	B	C	D	E	G
1	Cohort	Verification Code	Treatment Code	Treatment (duplicate of column C,)	Order (required by medrio)	Subject ID (to be filled in by UW CC and site pharmacy for tracking enrollment)
2	01	T1IL	GF66	GF66	1	
3	01	W93G	WE1W	WE1W	2	
4	01	XPKL	H5TT	H5TT	3	
5	02	R3S4	JKL1	JKL1	4	
6	02	E7FD	RRII	RRII	5	
7	02	KJ56	Y5TT	Y5TT	6	
8	03	YKLD	RU8E	RU8E	7	
9	03	E6F6	B4EE	B4EE	8	
10	03	EJU2	CT1L	CT1L	9	
11	04	VB8I	VV66	VV66	10	
12	04	NO09	Z1II	Z1II	11	
13	04	MNOP	PREW	PREW	12	

EXAMPLE 2: Un-blinded spreadsheet

	A	B	C	D	E	F	G
1	Cohort	Verification Code	Treatment Code	Treatment (duplicate of column C,)	Order (required by medrio)	Treatment Assignment (Avelumab or Placebo), available only to UNBLINDED staff	Subject ID (to be filled in by UW CC and site pharmacy for tracking enrollment)
2	01	T1IL	GF66	GF66	1	Avelumab	
3	01	W93G	WE1W	WE1W	2	Avelumab	
4	01	XPKL	H5TT	H5TT	3	Avelumab	
5	02	R3S4	JKL1	JKL1	4	Placebo	
6	02	E7FD	RRII	RRII	5	Placebo	
7	02	KJ56	Y5TT	Y5TT	6	Placebo	
8	03	YKLD	RU8E	RU8E	7	Avelumab	
9	03	E6F6	B4EE	B4EE	8	Avelumab	
10	03	EJU2	CT1L	CT1L	9	Placebo	
11	04	VB8I	VV66	VV66	10	Placebo	
12	04	NO09	Z1II	Z1II	11	Avelumab	
13	04	MNOP	PREW	PREW	12	Placebo	

For every randomized subject, there would only be a single possible combination of treatment code – verification code – cohort – treatment assignment allowed. This ensures that when a subject is randomized the same enrollment position is not filled by more than one subject.




Medrio System Administrator <no-reply@mail.medrio.com>
TEST Randomization Confirmation Site 01; 01-001-SND

A new query has been fired:
Study: ADAM Trial: Adjuvant Avelumab in MCC TEST

Query Details
Name: Randomization
Subject: 01-001-SND
Site: Site 01
Form: Randomization
Visit: Baseline Visit
Variable:Treatment_Code @ Baseline Visit Description Treatment Code: Y1LZ & Verification Code: 3L4J have been assigned for subject 01-001-SND in Cohort: 02 Created By: SYSTEM

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