

The Clinical Research Center

Research Practice Manual



Guideline for Developing Randomization Procedures – RPG-03

Guideline

Purpose

The purpose of this Guideline is to outline the Clinical Research Center's randomization procedures and the features of the randomization software used to construct the randomization schemata and related products required for a randomized, controlled trial.

Definitions

Randomization - the research method used in clinical investigations to assign study subjects to treatment or control groups using an element of chance to determine the assignment in order to reduce bias. (ICH GCP 1.48) "...assignment is made by chance, rather than by choice." (NCI Website).

Randomized controlled trial - The randomized controlled clinical trial (RCT) is considered the most reliable and unbiased method to evaluate if a treatment or intervention is effective. The RCT serves as the cornerstone of evidence-based medical practice.

CRC/CRIT Randomization software – a computer application that facilitates construction of a randomization schemata and related tools including randomization assignment lists and randomization envelope labels and inserts as needed. The randomization software used in the CRC was developed by the Clinical Research Information Technology (CRIT) team in collaboration with the CRC Biostatistics Core. The application is password protected and resides on a BCH network server housed in the CRC and maintained by the CRIT. Access is restricted to designated CRIT and CRC personnel.

The application generates random assignments to protocol specified treatment groups using a random permuted block design. This method serves to balance the treatment group assignments over the course of the study to ensure that the desired number of subjects will be allocated to each of the treatment groups at any time point during the randomization period. Typically, the senior statistician determines the block size. Permuted block sizes are not disclosed to the

blinded study personnel to minimize the likelihood of their being able to predict the next randomization assignment in the series.

The objectives of the randomization system are to:

- a) generate random assignments to treatment groups that are unpredictable and unique;
- b) provide users with an audit trail of the process including a verifiable link between subject ID and treatment assignment; and
- c) provide standard documentation tools including
 - o Subject ID Assignment Log,
 - o Master Randomization Assignment List,
 - o Investigator's (Site) Randomization Assignment List.

Randomization Envelope Labels and Inserts can also be provided when required by the randomization procedures appreciate for the protocol. Electronic distribution of randomization assignment lists, such as via a Sharepoint site, may also be utilized and may be most appropriate for multicenter trials. If this method is chosen, appropriate controls for access to only authorized pharmacists and unblinded study team personnel is essential.

Procedure

The following steps are completed during the CRC randomization service:

1. First, the randomization plan is jointly developed by the Principal Investigator (PI) and a Biostatistician and all specifications are described. The plan might be completely specified in the approved study protocol; if not, the details of the plan must be developed thereafter. The CRC provides a Randomization Checklist that facilitates this process (Attachment I).
2. The PI confirms the specifications for the randomization plan in writing by completing the Randomization Checklist (e.g., open trial vs. blinded trial, single blinded or double blinded; number of subjects to be randomized; number of study sites; number of treatment groups/arms; stratification factors; etc.).
3. A CRC Biostatistician approves the specifications and prescribes the size of the permuted block sizes.
4. With the approved specifications in hand, a CRC Project Manager or Data Manager inputs the specifications into the randomization software application.
5. The application generates the Master Randomization List (example shown in Attachment III) including all required random assignments in the specified permuted block design. All planned assignments are generated a priori.
6. The application also generates an Investigator's Randomization List (example shown in Attachment IV) for use by study personnel. This List is the same list as the Master List; however it does not include the randomized treatment assignments and block design. This 'blinded' list keeps study personnel blind to treatment assignments.

7. In a multi-site trial, separate Randomization Lists are customarily generated for each study site to ensure treatment group assignments are balanced within each site.
 - a. If the randomization design is stratified, separate Randomization Lists must also be generated for each stratum to ensure treatment group assignments are balanced within each stratum.
 - b. In addition, as appropriate, the Randomization List is maintained by the Project Manager and/or Biostatistician electronically, as well as in paper format. The paper document is signed and dated by the Biostatistician. The signed document and a .pdf version is then distributed to the site pharmacists.
8. As needed, the application can also generate, for each potential subject, a Randomization Envelope Label (example shown in Attachment V) and a Randomization Assignment Insert (example shown in Attachment VI) which can be opened by the study personnel at the appropriate time.
 - a. If envelopes are required, a CRC staff member prepares the randomization envelopes, i.e. a pre-printed, sequentially numbered label is affixed to an envelope and the matching, pre-printed insert is 'stuffed' into the envelope. An envelope is prepared in this manner for every potential subject on the Master Randomization Assignment List. Envelopes are sometimes used for open trial design studies, or single blind studies and occasionally for double blind studies. Even in an un-blinded study, to reduce bias, staff may use envelopes to reveal assignment so that they don't know the assignment ahead of time..
9. Prior to sealing the envelopes, an independent CRC staff member completes an audit of the prepared envelopes by comparing the envelope label against the corresponding insert and the Randomization Lists. Depending on the size of the study, all or some random sample of envelopes is audited. If errors are found in a random sample, then the audit is completed for all envelopes.

Description of Outputs

The randomization products developed for a clinical trial include a study specific Study ID Assignment Log, a Master Randomization Assignment List, and an Investigator's Randomization ID List. If required, the system can also produce Randomization Envelope Labels and Randomization Assignment Inserts. The products required for a randomization differ slightly depending on the study design. Here follows a description of procedures to follow for a double blind trial. Minor adjustments will be required for single blind and open trial designs.

1. Study ID Assignment Log: The Study ID Assignment Log is a simple Excel table with many rows of Study Subject ID numbers listed in column 1. Columns are provided to record the following: subject name, Site (i.e., BCH) medical record number, initials of person enrolling the subject, and date of enrollment. Frequently Investigators request columns to record the randomization #, date randomized, and initials of person randomizing. Other empty columns can be added on request. The Study ID Assignment Log documents the chronological enrollment of all subjects in the study. This essential document must be kept by the PI or designee in a locked file cabinet as it is the primary source document that links the subject's identity as well as medical record number to the confidential numeric study ID.

2. Master Randomization Assignment List: The Master Randomization Assignment List is organized in an Excel spreadsheet and includes rows of data for as many subjects expected to be randomized in the study. The following elements are provided for each row on the Master Randomization List:
 - 1) a Randomization number; and the associated 2) treatment condition assignment, and 3) permuted block number and block size. Empty columns are provided on the spreadsheet for recording the 4) subject's Study ID number, 5) the manufacturer's product, batch and/or lot number, 6) initials of the person completing the randomization and preparing the drug or treatment, and 7) the date of randomization.
3. The Master Randomization List for a double blind design must be kept by a neutral third party in a restricted access, locked file cabinet to ensure 1) blinded staff members are not inadvertently unblinded, and 2) compliance with human subject's protections regulations. The third party may include the Research Pharmacy, an unblinded Project Manager, a CTSU Nutritionist, or other independent individual. For the double blind drug trial, this List is typically kept in the Research Pharmacy. The PI and study staff should not have access to this List in a blinded trial.
4. Linking the randomization assignment to the Study ID: Strict compliance with documentation of randomization procedures is essential to ensure there is a reliable, verifiable link between the subject's study ID and the treatment assignment. The method for linking must be established a priori. Various procedures may be employed to establish the link. The most common method is described here:
 - a) The Randomization ID # is recorded on a study CRF and
 - b) The Master Randomization List, with all Study IDs and Randomization IDs and corresponding treatment assignments, is provided as an Excel file to the biostatistician who will analyze the data.
5. Investigator's Randomization ID List: The Investigator's Randomization ID List is a match to the Master Randomization Assignment List except it does not reveal the associated treatment assignments, block numbers or block sizes. Further, it will not include an empty column for recording drug product information. Customarily, the Investigator's Randomization ID List is kept by the Study Coordinator/PI.
6. Randomization Envelopes: Randomization Envelopes are frequently used in lieu of Randomization Lists for studies with open trial designs and single blind studies. This method allows unblinded study staff to open the very next envelope at the time of randomization to discover the subject's treatment assignment.

Envelopes may also be used in a double blind trial in addition to or in place of the Randomization Lists when procedural circumstances warrant their use. For example, an Investigator might request Envelopes if s/he anticipates a real possibility of serious adverse events related to the investigational agent such that s/he may need to 'break the

blind' urgently at a time when the Research Pharmacist is unavailable. In such a circumstance, Randomization Envelopes are kept in a locked location proximate to the PI or designee.

The following products will be provided if Envelopes are used for the study:

a) Randomization Envelope Labels: A Randomization Label is provided for placement on the outside of the randomization envelope. The label includes the study name, site name (if applicable) study PI name, the sequential Randomization number and additional text fields for hand recording the Subject ID number, and the date, time and signature of the person opening the envelope. A witness signature and date field may also be added to the back label.

b) Randomization Assignment Inserts: The Randomization Assignment insert includes the treatment assignment as well as all the same information that is on the outside envelope label.

Field Procedures for a Double Blind Trial Involving the Research Pharmacy

1. Assigning the Study ID: When a subject is enrolled in the study, s/he is assigned a confidential study identifier by adding his/her name to the very next empty row available on the Subject Study ID Assignment Log. See Example 1 below. The subject maintains this Study ID for the remainder of the trial and, thereafter, the Study ID is used on all research files, CRFs, Randomization Lists, Envelopes, and other research documents. In this example, subject Mary S. King is assigned the very next Study ID on the Log, i.e. Study # 01-03-5 by writing her name in the Subject Name column immediately next to the Study #. The subject's BCH (or Site) MR #, the enrollment date and initials of the person completing enrollment procedures are recorded in the remaining columns corresponding to the assigned Study ID # as well as the randomization information. In addition, additional columns may be included to indicate the subject status once it is determined the subject is eligible and has consented and enrolled, such as whether he or she was randomized (YES/NO) and if NOT randomized, the reason, such as withdrew participation. This is also documented on a case report form for each subject.

EXAMPLE 1: Subject Study ID Assignment Log

Subject Study ID Assignment Log

Study: Sample Randomization
Site: CHILDREN'S HOSPITAL BOSTON
PI: Jane Smith, M.D.

Enrollment					Randomization		
Study ID #	Subject Name (last, first, initial)	Subject MR#	Date Enrolled	Initials	Randomization #	Date Randomized	Initials
01-01-9							
01-02-7							
01-03-4							
01-04-9							
01-05-4							
01-06-0							
01-07-0							
01-08-7							
01-09-0							

2. Randomization: The Research Pharmacist will maintain the Randomization Log. Once the orders are received, the Research Pharmacist will assign the Randomization IDs to the study subjects. This will be maintained in real-time and it will never be completed retrospectively, e.g. patients can be randomized only after they are deemed eligible and have consented.
- Randomization IDs may never be reused due to the subsequent disruption it can make to the randomization.
 - Study Teams will not assign randomization IDs.

Research Pharmacy will keep the Randomization List/Log in a secure manner. Typically, the Log will include:

- Subject Name
- Study ID
- Medical Record Number (MRN)
- Manufacturer's Product Number
- Randomization ID#
- Treatment assignment
- Date Randomized
- Research Pharmacist/Staff Initials
- Additional information such as the Product Number may also be required, based on the study and treatment.

See “Randomization Procedure for Investigational Drug Service (IDS) in the Pharmacy Department Policy and Procedures Manual on the Children’s website for more detail.

Example 2: Master Randomization Treatment Assignment List/Log

STRATUM: Female								
Randomization #	Subject Name (last, first, initial)	CHB MR#	Study ID#	Treatment Assignment	Block Size	Manufacturer's Product #	Date Randomized	Initials
CH-F-1	<i>Bopper, Megan</i>	<i>CHB 13579</i>	<i>01-02-7</i>	Treatment	2	<i>XZ9.345</i>	<i>8/14/07</i>	<i>SA</i>
CH-F-2	<i>King, Mary S</i>	<i>CHB 16543</i>	<i>01-03-5</i>	Placebo	2	<i>XZ9.345</i>	<i>8/15/07</i>	<i>SM</i>
CH-F-3				Treatment	4			

3. Treatment Labeling and Drug Delivery: The PI or designee must meet with the Research Pharmacist early in the planning phase to develop the appropriate drug labeling and delivery plan. The Pharmacy procedures should be documented and maintained in the study manual of procedures and available to study staff involved in the randomization procedures. See the CRC Research Practice Guidelines for Developing Pharmacy Procedures for Clinical Trials (R10) for additional detail regarding development of your study pharmacy procedures.

Depending on the intervention, the study drug and placebo may be prepared in batches in advance or in real time when the actual randomization procedure takes place. The treatment might be delivered to the clinic or unit or the PI or Study Coordinator might pick it up in the Pharmacy. In any event, the study drug and placebo treatments (e.g. drug bottle, ointment tube, IV bag, etc.) must be labeled by Research Pharmacy such that subject identification can be verified when the treatment is delivered, distributed and administered in the clinical setting, i.e., the drug container or bag label should include the subject’s name and CHB medical record number and/or any other fail safe identifiers prescribed by Research Pharmacy requirements. In a double blind trial, the placebo treatment should be identical in appearance to the drug treatment.

See “Randomization Procedure for Investigational Drug Service (IDS) in the Pharmacy Department Policy and Procedures Manual on the Children’s website for more detail.

4. 24/7 Scheduling: Special arrangements will be required for obtaining study drugs or treatments for studies that aim to randomize subjects on a 24/7 schedule.
5. Breaking the blind: Unblinding rules must be established prior to the initiation of the protocol and discussed during Study Implementation/Start-up Meetings. Unblinding must be minimized to protect the integrity of the study. The authority to grant unblinding requests should be identified in the protocol and/or Manual of Operations. Typically, the Medical Monitor or PI will be the authority. Contact information for unblinding requests should be provided in protocol and/or Manual of Operations and maintained throughout the study. Any request to break a randomization must be put into writing; if any emergency situation, an email outlining the issue should suffice until a formal Note to

File is drafted. The proper authority (principal investigator, sponsor, etc.) must have authorized the requests and this person's name, as well as the person requesting the information, the time and date, and a note saying "unblinded" must be documented in the protocol.

6. If for any reason the PI must 'break the blind', s/he will need to contact the Research Pharmacist (or other pre-appointed staff associate) and ask for a report of the treatment assignment from the Master Randomization Treatment Assignment List. The blinded PI or designee should not have access to the Master List; rather the Research Pharmacist or other pre-appointed, unblinded person should ascertain the treatment assignment and report same to the PI. Envelopes are sometimes used in addition to Randomization Lists if the PI anticipates a real possibility of serious adverse events related to the investigational agent such that s/he may need to 'break the blind' urgently at a time when the Research Pharmacist or other appointed person may be unavailable. In such a circumstance, Randomization Envelopes are kept in a locked location proximate to the PI or designee.

Field Procedures for an Opened or Single Blind Trial Using Randomization Envelopes

The following procedures should be followed if Randomization Envelopes are used in lieu of Randomization.

1. When the subject is ready to be randomized, the Study Coordinator pulls the very next Randomization Envelope from the sequentially ordered Randomization Envelope file. (Note: Envelopes should never be drawn out of sequence for any reason.)
2. The Coordinator then records the requisite information on the Subject Study ID Assignment Log and/or the Investigator's Randomization List and, completes the Envelope Label (Shaded fields in Example 4). Finally, opens the envelope to review the Insert and ascertain the subject's treatment assignment. The empty fields on the Envelope Insert must also be completed. (Shaded fields in Example 5)

Example 3: Investigator's Randomization ID Assignment List

STRATUM: Female					
Randomization #	Subject Name (last, first, initial)	CHB MR#	Study ID#	Date Randomized	Initials
CH-F-1	Bopper, Megan	CHB 13579	01-02-7	8/14/07	JA
	King, Mary S	CHB 16543	01-03-5	8/15/07	S.M
CH-F-2					

Example 4: Envelope Labels

Study:	Trial of Sample Randomization
PI:	Jane Smith, M.D.
Site:	CHILDREN'S HOSPITAL BOSTON
Randomization #:	CH-F-2
Study ID#:	_____
Date envelope opened:	_____
Time opened:	_____
Person opening the envelope:	_____
Signature of Person Opening Envelope	_____
Note: Envelopes must be stored in a restricted access locked file	

Example 5: Randomization Assignment Insert

Randomization #: **CH-F-2** Treatment Assignment: **Placebo**

Study ID #: _____

Date envelope opened: ____ / ____ / ____

Time opened: ____ : ____ (24 hour clock)

H H M M

Signature of the person who is randomizing the subject:

1. The treatment assignment and other relevant randomization data should be recorded on the Randomization CRF and the opened envelope and corresponding insert should be filed in the restricted access study file along with the Subject ID Assignment Log.
2. An audit of envelopes and inserts should be completed routinely by a second staff person in real time or intermittently to verify correct treatment assignment. Customarily, an inspection of envelopes and inserts is completed by a Study Monitor during routine monitoring visit

Related documents can be found at

<http://chbshare.chboston.org/TS/resadmin/crp/Tool%20Box/Forms/AllItems.aspx>

Randomization Checklist

Study Name: _____

PI: _____

- What type of trial is it, a drug trial, treatment trial, or therapeutic / behavioral intervention?
- Is it an open trial design, a single blind or double blind design? *
- Does the study require an IND or IDE?
- What is the date for the start of enrollment?
- How many subjects will be enrolled? *
- What is the date for the start of randomization?
- How many subjects will be randomized? * (*Customarily, we provide randomization products sufficient to randomize your target plus 20%. Do you expect this number will be sufficient to accommodate drop outs?*)
- How long will enrollment take?
- What is the CCI approved protocol number? *
- What is the format for the confidential subject identification numbers? * [*CRP convention is one or more spaces for a site code, one or more spaces for a protocol number (if applicable), a unique subject ID number and a computer generated check digit, e.g. 01-02-004-8.*]
- Is there more than one site? *
 - ✓ How many sites are there? *
 - ✓ How many subjects will be randomized at each site? *
 - ✓ Name the sites and specify a preferred site code for each. *
 - ✓ We may need the name of the PI or designee for each site. *
- How many treatment/intervention arms are there? *
 - ✓ What are the treatment arms*?
 - ✓ Is either arm more heavily weighted than the other? *
- Will the randomization be stratified? *
 - ✓ Are some options expected to be more heavily represented than others? (e.g. 2 girls to each boy)? *
 - ✓ How many stratification factors are there? (e.g. gender, disease state, etc.)?
 - ✓ For each factor, how many levels/options are there? (e.g. race, age)? *
- If the trial is blinded, who is blinded to treatment assignment? *
 - ✓ Is the subject blinded? *
 - ✓ Is the PI blinded? *
 - ✓ Is the clinical provider(s) blinded? * If yes, who are blinded, MDs, RNs, Nutritionists?
 - ✓ Might there ever be an 'urgent' need to break the blind?
- Briefly describe the randomization procedures that will be required. *
 - ✓ Will every enrolled subject be randomized? *
 - ✓ How many minutes or hours will there be between the moment of randomization and the start of treatment? * (Is there time to contact pharmacy or CRP and get a call back with directives for the randomization?) (Are there special or cumbersome procedures to complete after randomization but before start of treatment/intervention?)
 - ✓ Will the Research Pharmacy require a list? *

* Information required for programming

Subject Study ID Assignment Log

Study: Sample Randomization
Site: CHILDREN'S HOSPITAL BOSTON
PI: Jane Smith, M.D.

Enrollment					Randomization		
Study ID #	Subject Name (last, first, initial)	Subject MR#	Date Enrolled	Initials	Randomization #	Date Randomized	Initials
01-01-9							
01-02-7							
01-03-4							
01-04-9							
01-05-4							
01-06-0							
01-07-0							
01-08-7							
01-09-0							

Master Randomization Assignment List

(Officer) Statistician: _____ Date: ____/____/____

Envelope QC (if applicable): _____ Date: ____/____/____

Study: Sample Randomization

Site: CHILDREN'S HOSPITAL BOSTON

PI: Jane Smith, M.D.

Generator: CRP Staff member

Stratum: Female

Randomization #	Subject Name (last, first, initial)	CHB MR#	Study ID#	Treatment Assignment	Block Size	Manufacturer's Product #	Date Randomized	Initials
CH-F-1				Treatment	2			
CH-F-2				Placebo	2			
CH-F-3				Treatment	4			
CH-F-4				Placebo	4			
CH-F-5				Placebo	4			
CH-F-6				Treatment	4			
CH-F-7				Treatment	6			
CH-F-8				Placebo	6			
CH-F-9				Placebo	6			

Investigator's Randomization ID List

(Officer) Statistician: _____ Date: ____/____/____

Study: Sample Randomization

Site: CHILDREN'S HOSPITAL BOSTON

PI: Jane Smith, M.D.

Generator: CRP Staff member

Stratum: Female

Randomization #	Subject Name (last, first, initial)	CHB MR#	Study ID#	Date Randomized	Initials
CH-F-1					
CH-F-2					
CH-F-3					
CH-F-4					
CH-F-5					
CH-F-6					
CH-F-7					
CH-F-8					
CH-F-9					
CH-F-10					
CH-F-11					
CH-F-12					
CH-F-13					
CH-F-14					
CH-F-15					
CH-F-16					

References

Children's Hospital, Boston, Clinical Research Center's Research Practice Guideline:
RPG-10 Guideline for Development of Pharmacy Procedures for Clinical Trials

Hulley SB, et al. *Designing Clinical Research: An Epidemiologic Approach*. 3rd ed. Philadelphia, PA: Lippincott, Williams & Wilkins; 2006

National Cancer Institute resource page. What is randomization? Available at:
<http://www.cancer.gov/clinicaltrials/learning/what-is-randomization>

The Clinical Research Center

Research Practice Manual



Document Attributes

Title	Guideline for Developing Randomization Procedures		
Author	Qiaoli Chen	Date of Origin	August 2010
Reviewed/ Revised by	Stavroula Osganian, MD, ScD, MPH	Dates Reviewed/Revised	4/10/2014; 1/20/2015
Copyright	©Boston Children's Hospital, 2015	Last Modified	1/20/2015
Approved	<u>SIGNATURE ON FILE</u> Stavroula Osganian, MD, ScD, MPH Chief, Clinical Research Center		

Disclaimer: Should Hospital and CRC policies conflict, Hospital policy will supersede CRC policy in all cases.