

## 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. 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 Subject ID Assignment Log, a Master Randomization Assignment List, and an Investigator's Randomization Assignment List. Randomization Envelope Labels and Inserts can also be provided when required by the randomization procedures appropriate for the protocol.

## 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 permuted block sizes.
4. With the approved specifications in hand, a CRC Project Director or Data Manager inputs the specifications into the randomization software application.
5. The application generates the Master Randomization List (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 (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.
8. 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.
9. As needed, the application can also generate, for each potential subject, a Randomization Envelope Label (Attachment V) and a Randomization Assignment Insert (Attachment VI) which can be opened by the study personnel at the appropriate time. 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, staff could use envelopes to reveal assignment so that they don't know the assignment ahead of time to reduce bias.

10. 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. For small studies, every envelope is audited. For large studies, an audit is completed for a ten percent sample of envelopes drawn randomly; if errors are found, 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. As 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 Subject ID numbers listed in column 1. All subsequent columns are blank for hand written recording of subject specific information as subjects are enrolled into the study. At a minimum, empty columns are provided to record the following: subject name, CHB 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 to the confidential 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. The Master Randomization List for a double bind 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, a GCRC

Nutritionists, or other independent individual. For the double blind drug trial, this List is typically kept in the Research Pharmacy.

3. 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.
4. 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 MR #, the enrollment date and initials of the person

completing enrollment procedures are recorded in the remaining columns corresponding to the assigned Study ID #.

**Example 1: Subject Study ID Assignment Log**

Study ID	Subject Name (last, first, initial)	Subject MR#	Date Enrolled	Initials
01-01-9	<i>Smith, Alex B</i>	<i>CHB 23456</i>	<i>8/10/2007</i>	<i>JA</i>
01-02-7	<i>Bopper, Megan</i>	<i>CHB 13579</i>	<i>8/12/07</i>	<i>JA</i>
01-03-5	<i>King, Mary S</i>	<i>CHB565432</i>	<i>8/15/07</i>	<i>SM</i>

1. Randomization: Randomization is a 2-step procedure. First, the Study Coordinator refers to the Investigator Randomization List to determine the Randomization #; then s/he contacts the research Pharmacy to report the Randomization # and initiate pharmacy randomization procedures.
  - a) Determining the Randomization #: When the subject is ready to be randomized, the Study Coordinator refers to the appropriate Investigator's Randomization Assignment List (e.g. correct site, correct strata); selects the very next Randomization # from the List, and records the subject information in the columns on the List corresponding to the Randomization #. In Example 2 below, Mary S. King, ID # 01-03-5 is assigned Randomization # CH-F-2 from the Investigator's Randomization ID Assignment List for the Female stratum. Her name, CHB MR #, and study ID# are recoded on the List. The date of randomization and initials of the person completing the randomization procedures are also recorded.

**Example 2: Investigator's Randomization ID Assignment List**

STRATUM: Female					
Randomization #	Subject Name (last, first, initial)	CHB MR#	Study ID#	Date Randomized	Initials
CH-F-1	<i>Bopper, Megan</i>	<i>CHB 13579</i>	<i>01-02-7</i>	<i>8/14/07</i>	<i>JA</i>
CH-F-2	<i>King, Mary S</i>	<i>CHB 16543</i>	<i>01-03-5</i>	<i>8/15/07</i>	<i>SM</i>
CH-F-3					
CH-F-4					

2. Determining Treatment Assignment: The Study Coordinator next contacts the Research Pharmacist to report the assigned Randomization # and initiate the pharmacy procedures. S/he reports to the Pharmacist, the Randomization ID #, subject's name, MR #, and Study ID. In turn, the pharmacist records these data on the appropriate row of the correct Master Randomization Assignment List along with the manufacturer's product ID, date randomized and his/her initials. In Example 3, the pharmacist records the subject's name, Mary S King, and her MR# and study ID number, 01-03-5 next to the assigned Randomization ID # (CH-F-2) on the Master Randomization Treatment Assignment List for the Female stratum. The pharmacist also records the manufacturer's product number, the date randomized and his/her initials to complete the row. Finally, the pharmacist prepares the placebo rather than study drug treatment for the subject.

### Example 3: Master Randomization Treatment Assignment List

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>XZJ.345</i>	<i>8/14/07</i>	<i>JA</i>
CH-F-2	<i>King, Mary S</i>	<i>CHB 16543</i>	<i>01-03-5</i>	Placebo	2	<i>XZJ.345</i>	<i>8/15/07</i>	<i>S.M</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 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.

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 Randomization IDs and corresponding treatment assignments is provided as an Excel file to the biostatistician who will analyze the data.
  
5. 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.
  
6. Breaking the blind: 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 4: Envelope Labels

Study:	Trial of Sample Randomization
PI:	Jane Smith, M.D.
Site:	CHILDREN'S HOSPITAL BOSTON
Randomization #:	<b>CH-F-2</b>
Study ID#:	_____
Date envelope opened:	_____

#### Example 5: Randomization Assignment Insert

Randomization #:	<b>CH-F-2</b>	Treatment Assignment:	<b>Placebo</b>
Study ID #:	_____		
Date envelope opened:	___ / ___ / ___		
Time opened:	___ : ___ (24 hour clock)		
	H H MM		

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



# The Clinical Research Center Research Practice Manual



## 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: \_\_\_ / \_\_\_ / \_\_\_\_\_

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**Study:** Sample Randomization

**Site:** CHILDREN'S HOSPITAL BOSTON

**PI:** Jane Smith, M.D.

**Generator:** CRP Staff member

**Stratum:** Female

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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					

## Randomization Envelope Labels

Study: Sample Randomization

PI: Jane Smith, M.D.

Site: CHILDREN'S HOSPITAL BOSTON

Randomization #: CH-F-1

Study ID #: \_\_\_\_\_

Date envelope opened: \_\_\_\_\_

Time opened: \_\_\_\_\_

Person opening the envelope: \_\_\_\_\_

Note: Envelopes must be stored in a restricted access locked file.

Study: 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: \_\_\_\_\_

Note: Envelopes must be stored in a restricted access locked file.

Study: Sample Randomization

PI: Jane Smith, M.D.

Site: CHILDREN'S HOSPITAL BOSTON

Randomization #: CH-F-3

Study ID #: \_\_\_\_\_

Date envelope opened: \_\_\_\_\_

Time opened: \_\_\_\_\_

Person opening the envelope: \_\_\_\_\_

Note: Envelopes must be stored in a restricted access locked file.

Study: Sample Randomization

PI: Jane Smith, M.D.

Site: CHILDREN'S HOSPITAL BOSTON

Randomization #: CH-F-4

Study ID #: \_\_\_\_\_

Date envelope opened: \_\_\_\_\_

Time opened: \_\_\_\_\_

Person opening the envelope: \_\_\_\_\_

Note: Envelopes must be stored in a restricted access locked file.

Study: Sample Randomization

PI: Jane Smith, M.D.

Site: CHILDREN'S HOSPITAL BOSTON

Randomization #: CH-F-5

Study ID #: \_\_\_\_\_

Date envelope opened: \_\_\_\_\_

Time opened: \_\_\_\_\_

Person opening the envelope: \_\_\_\_\_

Note: Envelopes must be stored in a restricted access locked file.

Study: Sample Randomization

PI: Jane Smith, M.D.

Site: CHILDREN'S HOSPITAL BOSTON

Randomization #: CH-F-6

Study ID #: \_\_\_\_\_

Date envelope opened: \_\_\_\_\_

Time opened: \_\_\_\_\_

Person opening the envelope: \_\_\_\_\_

Note: Envelopes must be stored in a restricted access locked file.

## Randomization Assignment Insert

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**Study:** Sample Randomization

**Site:** CHILDREN'S HOSPITAL BOSTON

**PI:** Jane Smith, M.D.

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**Randomization #:** CH-F-1

**Treatment Assignment:** Treatment

**Study ID #** \_\_\_\_\_

**Date envelop opened:** \_\_\_ / \_\_\_ / \_\_\_

**Time opened:** \_\_\_ : \_\_\_ (24 hour clock)  
H H M M

**Signature of the person opening the envelope:** \_\_\_\_\_

## 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*. 3<sup>rd</sup> 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>

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