Understanding the Randomization Process –
Standard Procedures and Documentation

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• Course Director and Course Planners, Kevin Tracey, MD, Cynthia Hahn, Emmelyn Kim, MPH, Tina Chuck, MPH have nothing to disclose.
• The speakers, Martin L. Lesser, PhD and Meredith Akerman, MS have nothing to disclose.
What is a Randomized Clinical Trial?

• A Randomized Clinical Trial (RCT) is a type of experimental design whereby experimental units (e.g., subjects) are randomly assigned to a treatment condition.

• Random assignment is said to occur when every subject has the same probability of being assigned to a given treatment as any other subject AND each subject’s assignment is independent of any other subject’s assignment.
Features of Randomization

- It eliminates bias in treatment assignment, specifically selection bias and confounding.
- It facilitates blinding (masking) of the identity of treatments from investigators, subjects, and evaluators.
- It permits the use of probability theory to express the likelihood that any difference in outcome between treatment groups merely indicates chance.
Why this Course?

• To better understand the randomization process in the context of Good Clinical Practice (GCP)
• To better understand the importance of documentation of treatment assignment in order to maintain data integrity
• To better understand how to make the randomization process accountable and audit worthy
Motivation for this Course: Audit Findings

• Randomization process was not well described at the start of the study
• Violation of randomization process: protocol stated use of “envelope method” but “telephone method” was used
• Randomization process was not well designed, resulting in a large imbalance between the two treatment groups
• PI did not have adequate staff or delegate appropriate personnel to perform the randomization. Pharmacist/ coordinator was not trained on the randomization procedure
• Documented treatment did not match the randomization assignment
• Documentation does not support whether subjects received the correct treatment
• Protocol was not amended when the randomization process was changed
• PI did not know where to get randomization assistance
Types of Randomization

• Fixed Allocation Randomization
  ➢ Randomization probabilities remain constant throughout the study

• Adaptive Randomization
  ➢ Randomization probabilities change over the course of the study
Mechanics of Fixed Allocation Randomization
Simple Randomization

• Repeated “toss of a coin” with prob(Heads)=p
• Coin toss is simulated via a computer algorithm
• Typically, p=0.5, but p can be any value between 0 and 1
• Unbalanced randomization (p ≠ 0.5) is sometimes used
• Examples of possible sequences outcomes under simple randomization:
  - ABABABABABBBAAABABAABAB  (A=10; B=10) – balanced
  - AABBBAAABABBAABBAAAAA  (A=12; B=8) – moderately unbalanced
  - AAAAAAAAAABBBBBBBBBAAAAA  (A=19; B=1) – very unbalanced
Advantages and Disadvantages of Simple Randomization

• **Advantages**
  - Easy to implement
  - Easy to understand

• **Disadvantages**
  - At any point in the randomization there could be a substantial imbalance, specifically if sample size is small, which can reduce ability (power) to detect true differences between groups
    - *NOTE*: Imbalance does not imply lack of randomization
Permuted Blocks Randomization (PBR)

- PBR helps to avoid unbalanced randomization sequences
- A "block size" and "allocation ratio" (number of subjects in one group versus the other group) are specified, and subjects are allocated randomly within each block
- Examples of permuted block randomization:
  - B=1  AAAABABAAAAAAABBB  (11 A, 5 B)
  - B=2  AB AB BA AB AB BA AB BA  (8 A, 8 B)
  - B=4  ABBA AABB BABA BABA  (8 A, 8 B)
  - B=6  AABABB ABABBA AAAB  (9 A, 7 B)
- **NOTE 1**: Avoid alternating randomization, even though it assures balance.
- **NOTE 2**: Example B=2 is not alternating randomization.
Advantages and Disadvantages of Permuted Blocks Randomization

• **Advantages**
  - (Approximate) balance between the number of subjects in each group is guaranteed during the course of randomization
  - If the trial should be terminated early, balance will exist in terms of number of subjects randomized to each group
  - Blocking increases the power of the study because it guarantees balance

• **Disadvantages**
  - If the blocking factor is known by the study staff and the study is not double-blind, the assignment of the last subject entered in each block is known before randomization of that subject
Mechanics of Adaptive Randomization
Adaptive Randomization

• Change the allocation probabilities as the study progresses

• Two types:
  1. Baseline Adaptive Randomization
  2. Response Adaptive Randomization
Baseline Adaptive Randomization

• Adjust or adapt the allocation probabilities according to imbalances in numbers of subjects or in baseline characteristics between the two groups

• “Biased coin” method
  - Attempts to balance the number of subjects in each treatment group based on the previous assignments, but does not take subject responses into consideration
Advantages and Disadvantages of Baseline Adaptive Randomization

**Advantages**
- The investigator cannot determine the next assignment by discovering the blocking factor
- Protects against a severe baseline imbalance for important prognostic factors

**Disadvantages**
- It is operationally more difficult to carry out, especially if a large number of factors are considered. Because of its complexity, it is not as widely used as the permuted blocks randomization scheme
Response Adaptive Randomization

• Adjust allocation probabilities according to the responses of subjects to the assigned intervention
  • Play the Winner – stay with the winner until a failure occurs and then switch
  • Two-Armed Bandit – continually updates the probability of success as soon as the outcome for each subject is known
Advantages and Disadvantages of Response Adaptive Randomization

• **Advantages**
  - Maximizes the number of subjects on the “superior” intervention

• **Disadvantages**
  - The possible imbalance will almost certainly result in some loss of power and require more subjects to be enrolled into the study than would a fixed allocation with equal assignment probability
  - Many RCTs do not have an immediately occurring response variable
  - RCT may have several response variables with no single outcome easily identified as being the one upon which randomization should be based
Stratification

- Randomization does not guarantee that prognostic factors will be evenly distributed between treatment groups (except in very large trials)
- Prognostic factor imbalance may result in confounding, thus biasing the results
- Imbalance can be partly addressed by stratification prior to randomization
- Imbalance can also be addressed by covariate adjustment at the time of analysis
Stratification: An Example

**NO STRATIFICATION**

Randomize

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<th>High Risk</th>
<th>Response Rate</th>
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<tr>
<td>Chemo</td>
<td>27 (30%)</td>
<td>62 (70%)</td>
<td>89</td>
</tr>
<tr>
<td>RT</td>
<td>56 (80%)</td>
<td>38 (20%)</td>
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<tr>
<td></td>
<td>83</td>
<td>100</td>
<td>183</td>
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Observed difference is confounded by the prognostic factor

**RANDOMIZE WITHIN STRATA**

Randomize within Low Risk n=83

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<td>Chemo 25%</td>
</tr>
<tr>
<td></td>
<td>43 (46%)</td>
<td>RT 64%</td>
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Randomize within High Risk n=100

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<tbody>
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<td>Chemo RT</td>
<td>49 (55%)</td>
<td>Chemo 25%</td>
</tr>
<tr>
<td></td>
<td>51 (54%)</td>
<td>RT 64%</td>
</tr>
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</table>

Observed difference is not confounded by the prognostic factor
Blinding of RCTs

- **Open-label** – both the subject and the study staff know the treatment assignment
- **Single Blind** – only subjects are blinded to treatment assignment
- **Double Blind** – neither the subjects nor the study staff know which subject are receiving which treatment
- “**Double Dummy**” – all subjects receive both administrations of treatment but one is active and one is placebo
Concealed Allocation

• A procedure implemented in a RCT where the individuals treating and evaluating subjects are unaware of the next subject’s treatment assignment.

• Concealed allocation reduces the chance of deliberately excluding a subject based on how they might behave or respond on the impending assignment.
Special Considerations (1)

• Cluster randomized trials
  – Hospitals or practices are randomized to treatment, not individuals
Special Considerations (2)

- Crossover designs
  - The randomization and allocation are given as AB or BA for a two-period crossover trial
Special Considerations (3): Precautions with Double Blinded Studies

• Quality control for double blind medication distribution prior to implementing randomization

• Lot number randomization
Special Considerations (4): Randomization Errors

• Ineligible
• Wrong stratum
• Withdrawal of consent
  – Prior to randomization
  – After randomization

** Consider “Intention-to-Treat” (ITT)
** Consult with the statistician
Documentation

• Development of the step-by-step documentation of the randomization procedure
  – Importance (consistently, correctly)
  – Who is the authorized caller?
  – Who performs the randomization?
  – What information is exchanged?
  – When does it happen?
  – Where does it take place?

• Proper recording of treatment assignments
  – Record computer allocation when it’s generated
  – Record subject information including ID number, date of randomization, etc.
Randomization Procedures

Introduction: This document explains the process of randomizing subjects to the "Treatment Group" or "Standard of Care Group" in the study entitled "TITLE OF THE STUDY" (IRE #xx-yyyy)

1. Subjects will be approached to participate in the study and informed consent will be obtained. The subject will then be randomized and enrolled into the study.

2. The investigator, at his/her convenience, will phone the Biostatistics Unit (516-562-9300) during normal business hours (Monday-Friday, 9am-5pm) in order to randomize the subject. The caller will notify the person answering the phone (the Randomizer) in Biostatistics that he/she wants to randomize a subject into the "TITLE OF THE STUDY" protocol (IRE #xx-yyyy)

3. The Randomizer retrieves the appropriate randomization log book.

4. The caller provides the following information to the Randomizer:
   4.1. Subject’s year of birth
   4.2. Name of caller requesting randomization

5. The Randomizer will consult the randomization book and will locate the next available randomization sequence number. [Previously randomized subjects will have been logged onto the form and the current subject will be randomized according to the next blank line on the log]

6. The Randomizer will enter items 4.1 and 4.2 (Year of Birth and caller’s identity), as well as the Date of Randomization and the Randomizer’s initials, in the space provided on the randomization list.

7. The Randomizer will inform the caller of that subject’s randomization assignment, which will be one of the following two possibilities:
   - Treatment Group
   - Standard of Care Group

8. The Randomizer will inform the caller of the subject’s unique randomization sequence number, having the format ‘yyy’, which will be numbered sequentially starting with ‘001’.

9. The Randomizer and the caller will terminate the call.

10. The Randomizer will then fill out the randomization confirmation sheet. The Randomizer will scan this form to the Randomizer’s e-mail address.

11. The Randomizer will forward this e-mail to the following people with the subsequent subject line:
    - Subject line: TITLE OF STUDY randomization notification
    - E-mail recipients

12. The Randomizer will file the confirmation form in the randomization book and will enter the date of e-mail confirmation onto the subject’s log page in the space provided.

13. Upon receipt of the confirmation form, the Investigator will log this information into his/her copy of the randomization book and file the confirmation. This completes the randomization process.

END OF RANDOMIZATION PROCEDURE
### Randomization List

**Title of the Project**  
**Name of Principal Investigator**

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<thead>
<tr>
<th>Randomization Sequence #</th>
<th>Date of Randomization</th>
<th>Year of Birth</th>
<th>Group</th>
<th>Last Name of Caller</th>
<th>Last Name of Randomizer</th>
<th>E-mail Confirmation Date</th>
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**The Feinstein Institute for Medical Research**
Implementation of Randomization Procedure

- Phone call to central statistical office
- Phone call to pharmacy
- Envelope method
- Web-based randomization system
- Interactive Voice Randomization System (IVRS)
Record Keeping

• Preparation of double-blinded medication
• Blinded vs. Unblinded logs
• Confirmation procedure
• Ability to break the blind
• Actual treatment received should be perfectly auditable
ALCOA – the Standard of the Documentation

**Attributable**
- It should be obvious who created a record, and when it was created
- If a record was changed, it should be obvious who made the change,
- when the change was made, and why

**Legible**
- The research record should be easily read

**Contemporaneous**
- Study evidence/results should be recorded as they are observed
- All signatures/initials should be attached to a date indicating when the
- signature was added to the document

**Original**
- Study records should be originals, not photocopies

**Accurate**
- Study records should have a high level of integrity and honesty to what
- was truly observed; give a full accounting of the research process
- Study records should be thorough and correct; double check your work
- for unintentional errors
Summary

• Many ways to perform randomization depending on the needs of the trial
• Ways not to do randomization
• Documentation of the process is essential during the conduct of the study
• Documentation of actual treatment assignments is essential with special consideration in double blinded studies.
• A statistician should be involved in all randomized trials (specifically in stage II, III, and IV trials)