Memorial Sloan Kettering
Cancer Center

Randomization: An Overview and its Role at MSKCC

Clinical Trials Course

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What is Randomization?

- Definition: The selection of subjects or samples for each 'arm' of a study or experiment based on chance alone, i.e., a theoretical coin toss.

Why is randomization important in clinical research?

- Each trial participant has the same chance of receiving any of the trial treatments
- Important characteristics are similar across arms except for treatment effects
  - This means that at the end of the study, observed differences between groups can be attributed to the intervention, rather than to potential differences in observed and unobserved characteristics

Clinical Equipoise

- Clinical equipoise is the most widely accepted ethical justification for randomized trials
- Requires general uncertainty or disagreement about the relative merits of two or more therapies within the expert medical community
- Entails two principles
  - Honest null hypothesis
  - Participants should not receive a treatment inferior to what is available in clinical practice

Types of clinical research studies using randomization

- Pilot
- Phase II
- Phase III: randomized controlled trials are the gold standard of clinical research

Ethics of placebo controls

- Placebo controls are considered acceptable when there is a methodological justification for using a placebo and the trial fulfills ethical considerations concerning risk

Ethics of randomized placebo-controlled trials (RPCT) in oncology

- Placebo-controlled randomized trials are ethical in some cases
- Methodological justification exists if patients have cancer (typically metastatic disease) for which no approved, effective therapy exists or the treatments available are minimally effective and/or present serious adverse events
- In these cases, providing optimal palliative care without additional anticancer therapy is reasonable and ethically preferable

Randomization Logistics

- Non-blinded
- Blinded
  - Full or Double-blinded
  - Single-blinded
  - Partially-blinded
- Clustering (by clinic, by surgeon, etc.)
- Allocation ratio (1:1, 2:1, etc.)

Randomization Methods

- Simple randomization
- Randomly permuted block randomization
- Stratified randomly permuted block randomization

Simple Randomization

- Flipping a coin
- Works in principle for large studies
- Potential for imbalance in both arms and patient characteristics for smaller studies

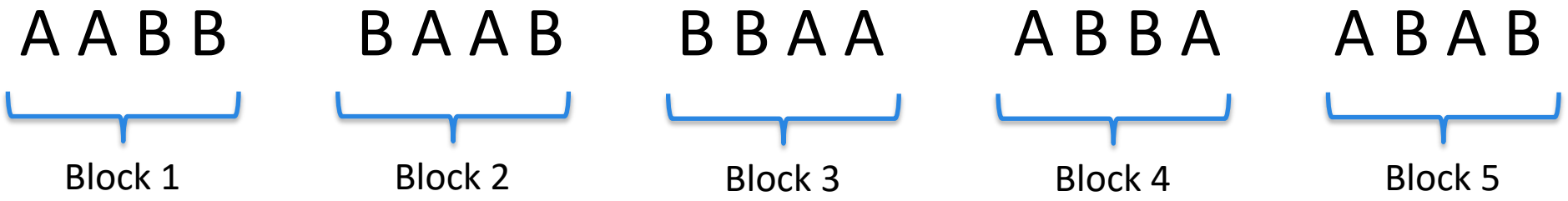
A B A A B B B B A B A B A A B

Randomly Permuted Block Randomization

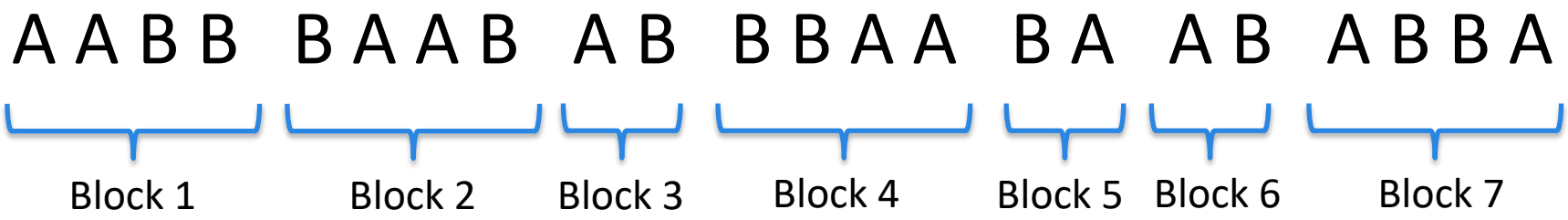
- Randomly allocate patients to a treatment arm while maintaining balance across treatment arms
- Block sizes are in multiples of the number of arms and take the allocation ratio into account
- Block size
  - Fixed size
  - Random size based on a maximum size
- Block size is not stated in protocol to maintain allocation concealment

Randomly Permuted Block Randomization

- Example for a 20-patient study with 2 treatments A and B allocated 1:1 using a fixed block size of 4



- Example for a 20-patient study with 2 treatments A and B allocated 1:1 using a random block size of max 4



Stratified Randomly Permuted Block Randomization

- Stratification groups patients by important clinical characteristics that may impact the success of the treatment
- Achieve balance of treatments within strata
- Randomization works independently among strata
- Within each stratum, randomly permuted blocks

Stratified Randomly Permuted Block Randomization

- Example for a large study with 2 treatments A and B allocated 1:1 using a fixed block size of 4. Patients are stratified by 2 variables: gender (male or female) and age group (<=50 years old or >50 years old)
- With 2 stratification variables each with 2 categories, there are 2x2 strata
  - Female, <=50 years old
  - Female, >50 years old
  - Male, <=50 years old
  - Male, >50 years old

Stratified Randomly Permuted Block Randomization

- Female, <=50 years old

Block 1	Block 2	Block 3	Block 4	Block 5
A B A B	B A B A	B A A B	A B A B	A B A B

- Female, >50 years old

Block 1	Block 2	Block 3	Block 4	Block 5
A A B B	B A A B	B B A A	A B B A	A B A B

Stratified Randomly Permuted Block Randomization

- Male, <=50 years old

Block 1	Block 2	Block 3	Block 4	Block 5
B A B A	B B A A	B B A A	A B B A	A B A B

- Male, >50 years old

Block 1	Block 2	Block 3	Block 4	Block 5
A B B A	B A A B	A A B B	A B A B	B B A A

Intent to Treat

- Patients are analyzed in the arm to which they were randomized regardless of treatment received
- Modified Intent to Treat
- No patient “replacement” in randomized studies
- Intent to Treat vs Per Protocol Analysis

The Role of Randomization at MSKCC

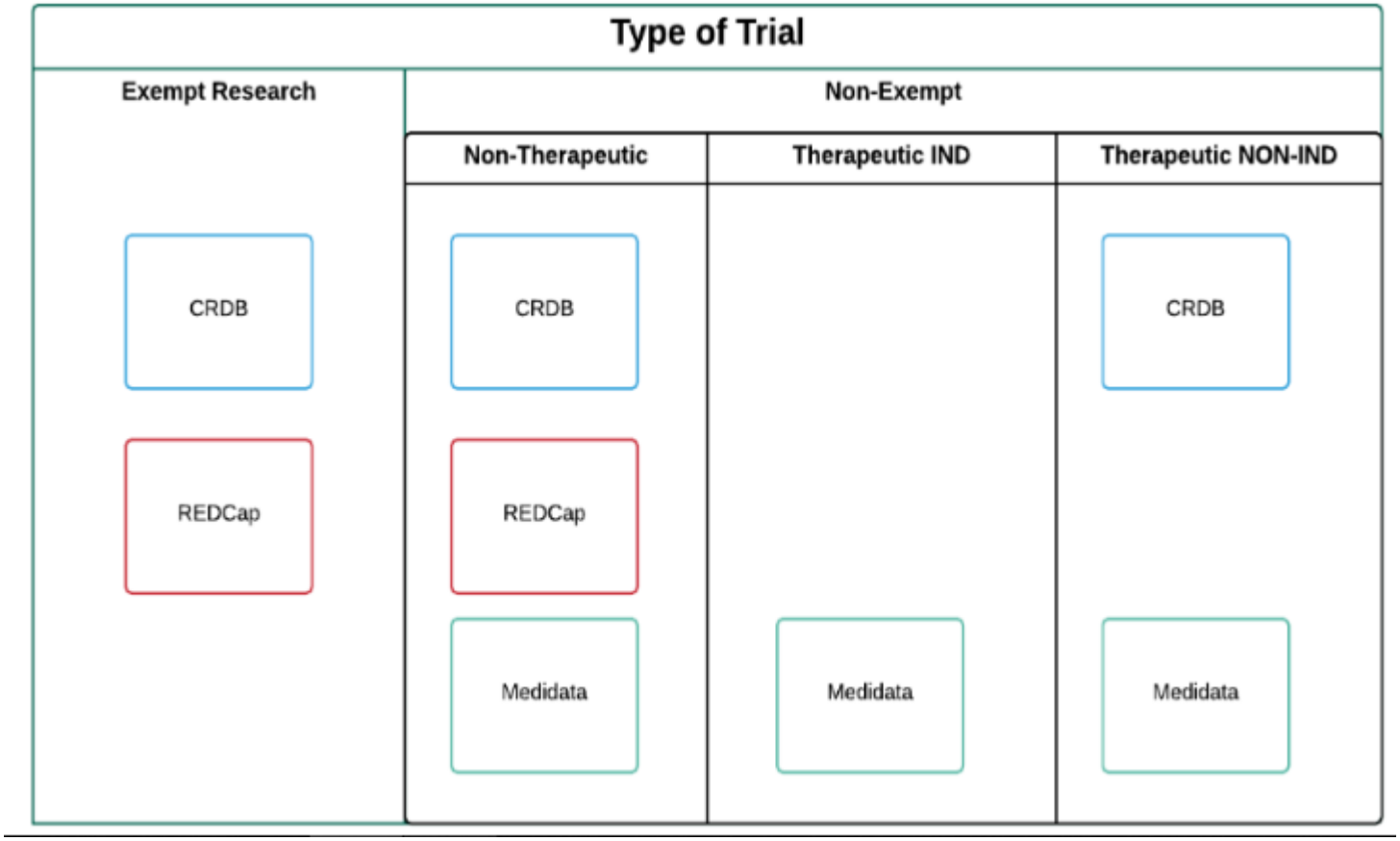
CRDB and CTMS

- Historically, patient registration and randomization were performed through the **Clinical Research Database (CRDB)** by the centralized Office of Clinical Research (OCR)

- After the adoption of the **Clinical Trials Management System (CTMS)**, patient registration and randomization are decentralized, allowing the study team to register participants through CTMS and randomize using a CRDB module

- In practice this means that there is one system for performing the randomization (CRDB) and a separate system for tracking the randomization and other components of registration (CTMS)

Electronic Data Capture Systems



Here we describe the MSK clinical research EDC systems that are available and strongly recommended by the Center: 1) REDCap, 2) CRDBi, and 3) Medidata Rave. Using one of these three supported data collection and analysis systems ensures that your data will be backed up appropriately, integrated across the other EDC platforms, and integrated with other research and institutional systems/initiatives (Information Systems, PIMS, CRDB, CRDBi, etc.).

Randomized Studies at MSKCC

- Study types
  - Unblinded (N~50)
  - Blinded (N~10)
- Mechanisms of randomization
  - CRDB (N~60)
    - Ideal mechanism which we prioritize
  - REDCap (N~10)
    - CRDB exemptions are specific to the design and setting of the trial
    - REDCap-randomized studies are typically not patients (e.g., study of taxi drivers) and are not therapeutic (e.g., intervention is educational)
  - Cluster randomized (N<10)
    - Randomization schema generated by randomization team

Example of an unblinded, CRDB randomized MSK Study

23-145

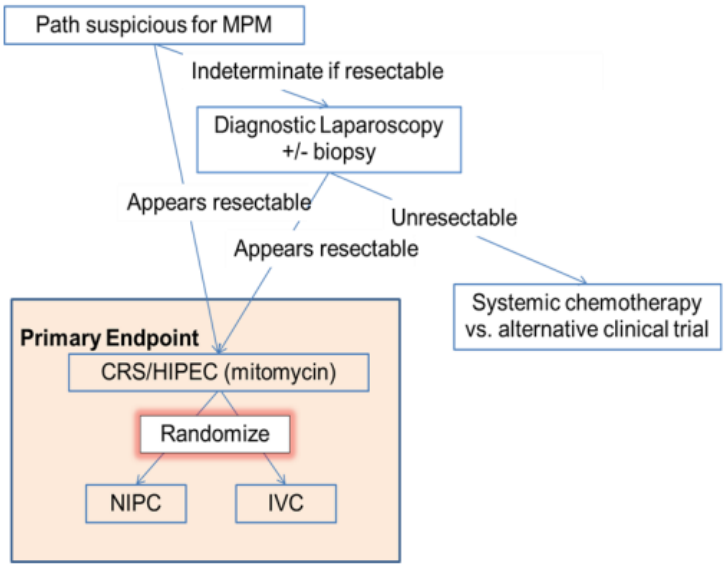
MSK PROTOCOL COVER SHEET

ICARuS II (Intraperitoneal Chemotherapy After cytoReductive Surgery): A multi-center, randomized phase II trial of normothermic intraperitoneal chemotherapy and intravenous chemotherapy after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma

7.2 Randomization

Patients will be randomized (1:1) to either arm A (NIPC) or arm B (IVC) postoperatively following CRS with HIPEC. After eligibility is established and consent is obtained, patients will be registered through the Clinical Trials Management System (CTMS) and then randomized using the Randomization Module in the Clinical Research Database (CRDB) in the operating room after determining that cytoreduction will be complete. Randomization will be accomplished by the method of random permuted block, and patients will be stratified by the initial peritoneal carcinomatosis index (low PCI or high PCI), the completeness of cytoreduction (optimal or sub-optimal) and gender (male or female). The Clinical Research Coordinator at MSK will be responsible for executing the process for all sites. The MSK research staff will notify the enrolling site of their participant's randomization assignment via e-mail.

Schema



Example of blinded, CRDB randomized MSK Study

23-022

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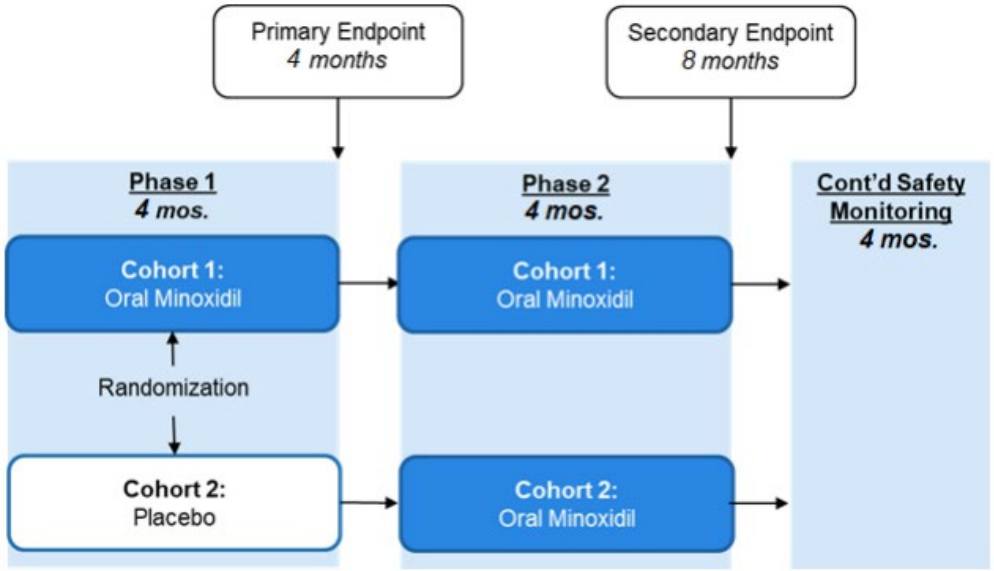
MSK PROTOCOL COVER SHEET

A pilot study of oral minoxidil for the treatment of persistent hair loss in pediatric, adolescent, and young adult cancer survivors

7.2 Randomization

Patients will be randomized to receive low-dose oral minoxidil or placebo followed by low-dose oral minoxidil in a 1:1 fashion. After eligibility is established and immediately after consent is obtained, patients will be registered in the Clinical Trials Management System (CTMS) and randomized using the Clinical Research Database (CRDB). Randomization will be accomplished by the method of random permuted block. The only stratification factor is the type of treatment that induced the alopecia (prior cranial radiation ± chemotherapy versus chemotherapy). Since this is a double blind study, the patients' treatment assignments can be viewed in the CRDB only by the hospital pharmacists who are dispensing the study drugs.



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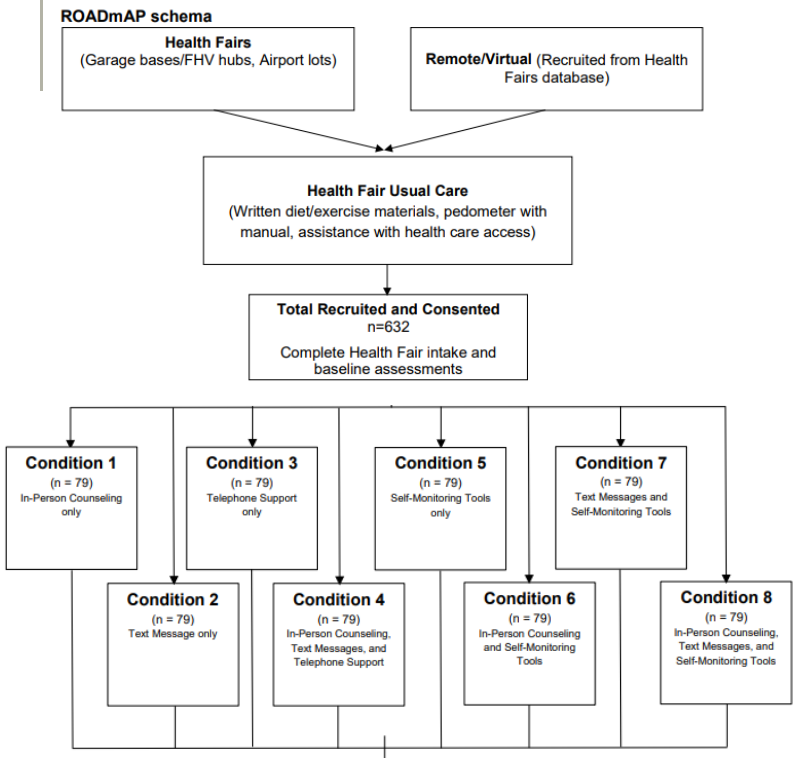
Example of REDCap randomized MSK study

15-088

MSK PROTOCOL COVER SHEET

COMIDA: Consumo de Opciones Más Ideales De Alimentos
(Consumption of More Ideal Food Options)



12.2 Randomization

For SANOS, the randomization will be stratified by gender and BMI (<30, 30 to 34.9, and ≥35 kg/m2), and for ROADMAP, the randomization will be stratified by marital status (yes/no to married/partnered), and hours worked per week (≤ 55 hours, > 55 hours), to maximize balance. For Family COMIDA, the randomization will be stratified by gender only (as BMI data will not be immediately available).

Study enrollees will be randomly assigned to a study arm via a generated list. Once the participant is consented to the study, the consenting professional will sequentially assign the participant to the intervention arm identified in the randomization list, provided by the Department of Epidemiology and Biostatistics at MSK using a computer program, REDCap, to generate the list of randomization assignments, stratified by gender and BMI for SANOS, gender only for Family COMIDA, and marital status and hours worked per week for ROADmAP.

Example of cluster randomized MSK Study

25-079

MSK PROTOCOL COVER SHEET

Breast Reconstruction Decision Aid (RECONJOINT)

Principal Investigator/Department: Evan Matros / Plastic and Reconstructive Surgery

PROTOCOL SUMMARY AND/OR SCHEMA

The primary objective of this study—"Breast Reconstruction Decision Aid (RECONJOINT)"—is to determine the feasibility of conducting a multi-institutional hybrid effectiveness-implementation study to evaluate the effectiveness of a decision aid (RECONJOINT) for breast reconstruction. To do this, we will conduct a pilot cluster-randomized, randomized controlled trial (RCT) at two sites, Duke University and MSK. Ultimately, this effort will determine the feasibility of our future larger-scale RCT and will identify any barriers to trial implementation before conducting the larger RCT.

- Patients in the intervention group will complete the decision aid before their consultation with the reconstructive surgeon, and both the patient and the provider will then have access to the results of the decision aid, which displays what aspects of surgery were most important to the patient in their decision-making process.
- Patients in the control group will not have access to this information, as they will not complete the decision aid.

7.2 Randomization

Participating surgeons will be randomized to Enhanced Usual Care or Intervention with a 1:1 ratio. Randomization will be stratified by study site. A list of randomized assignments is prepared and managed by the MSK Biostatistics Service and provided to the PI and study team. Randomization assignments will be disseminated via email. Clusters will be randomized by permuted block randomization into one of the two intervention conditions (Enhanced Usual Care or Intervention).

Responsibilities of Randomization Team

- After protocol is approved: Set up randomization procedure in Clinical Research Database (CRDB) and Clinical Trials Management System (CTMS)

- After protocol begins accrual: Monitoring

- Annually: Provide randomization allocations for interim analyses at the DSMB annual meeting

Randomization Considerations

For PI, Study Statistician, and Protocol Team:

- Is the study blinded?
- How many arms are there? What is the allocation to each arm (e.g., 1:1)?
- How many strata are there?
  - How many levels are there within each strata?

For Randomization Team:

- Appropriate block size (somewhat subjective)
  - If too small and the study is unblinded, the study team may be able to guess the next treatment assignment
  - If too large, balance may not be achieved at the end of the study

Sample Text for a Randomized Protocol

CRDB Unblinded Randomization

Patients will be randomized to: [specify arms]. After eligibility is established and immediately after consent is obtained, patients will be registered in the Clinical Trials Management System (CTMS) and randomized using the Clinical Research Database (CRDB). Randomization will be accomplished by the method of random permuted block, [and patients will be stratified by the variable(s) ……]

CRDB Blinded Randomization

This is a double blind randomized comparison of [specify arms]. After eligibility is established and immediately after consent is obtained, patients will be registered in the Clinical Trials Management System (CTMS) and randomized using the Clinical Research Database (CRDB). Randomization will be accomplished by the method of random permuted block, [and patients will be stratified by the variable(s) ……]. Since this is a double blind study, the patients' treatment assignments can be viewed in the CRDB only by the hospital pharmacists who are dispensing the study drugs.

Cluster Randomized

Participating [sites/surgeons/unit of clusters] will be randomized to [arm 1] or [arm 2] with a [1:1] ratio. Randomization will be stratified by [stratification factors]. A list of randomized assignments is prepared and managed by the MSK Biostatistics Service and provided to [study team to specify who receives this information]. Randomization assignments will be disseminated via [dissemination method]. Clusters will be randomized by permuted block randomization into one of the [two] intervention conditions ([arm 1] vs [arm 2]).

Contacts and References

- zzPDL_BST_RandomizationsBiostatisticians@mskcc.org
  - Elyn Riedel
  - Anne Reiner
  - Jessica Lavery
- The randomization and stratification of patients to clinical trials, Zelen 1974
- Information on the Clinical Research Database (CRDB)
- Information on the Clinical Trials Management System (CTMS)
- Web Protocol System