

Designs for Clinical Trials

Design and Analysis of Clinical Trials Concepts & Methodologies
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Designs for Clinical Trials

Parallel design

Crossover design

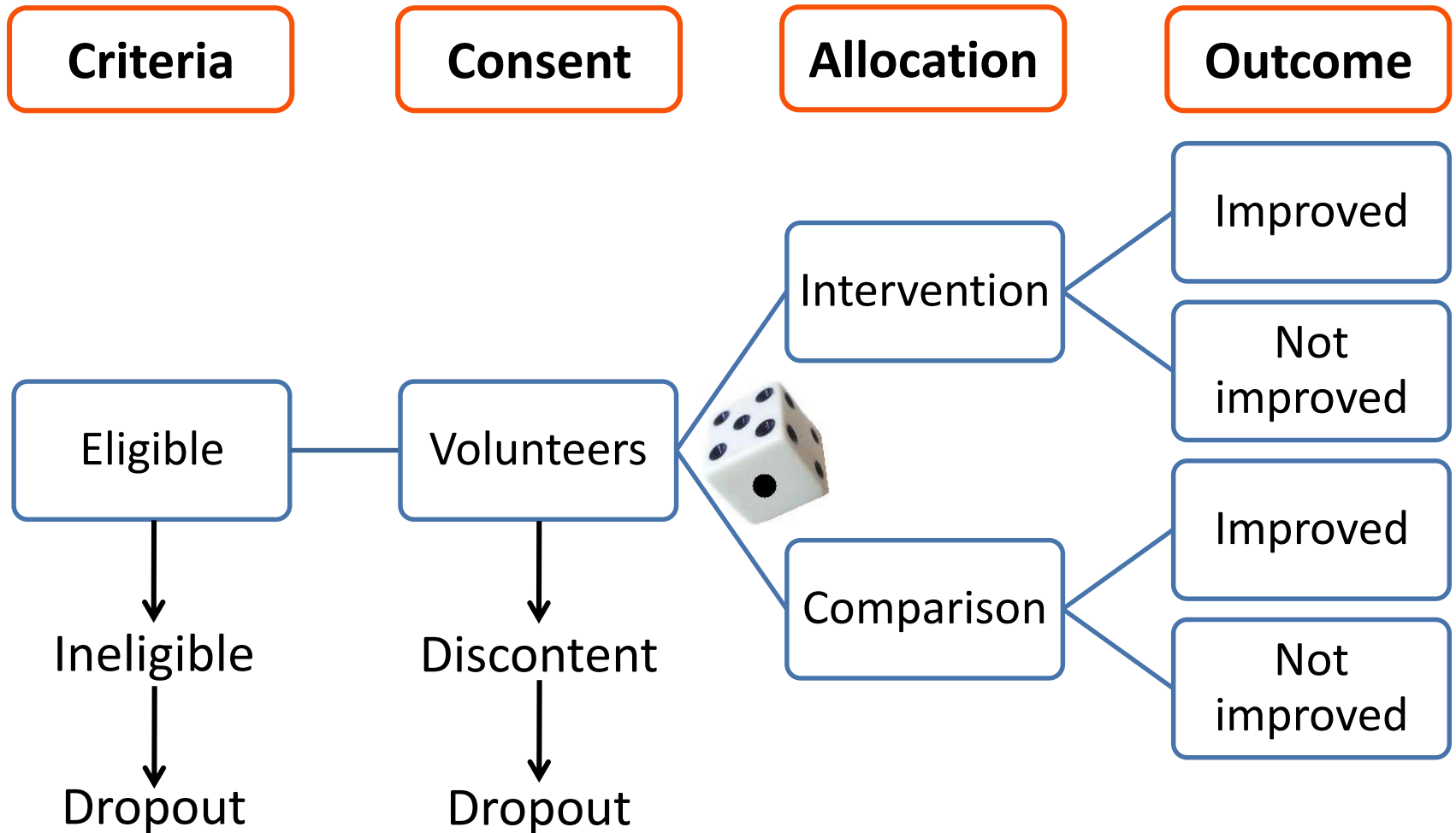
Factorial design

Clustered Randomized Design

Multi-center trials

- ❖ Appropriate design or the optimal design depends on the objective of the clinical trial.

Parallel Design



Parallel Design

❖ Advantages

- Simple and easy to implement
- Universally accepted
- Applicable to acute and chronic conditions
- Analysis is less complicated
- Interpretation of the results is straightforward

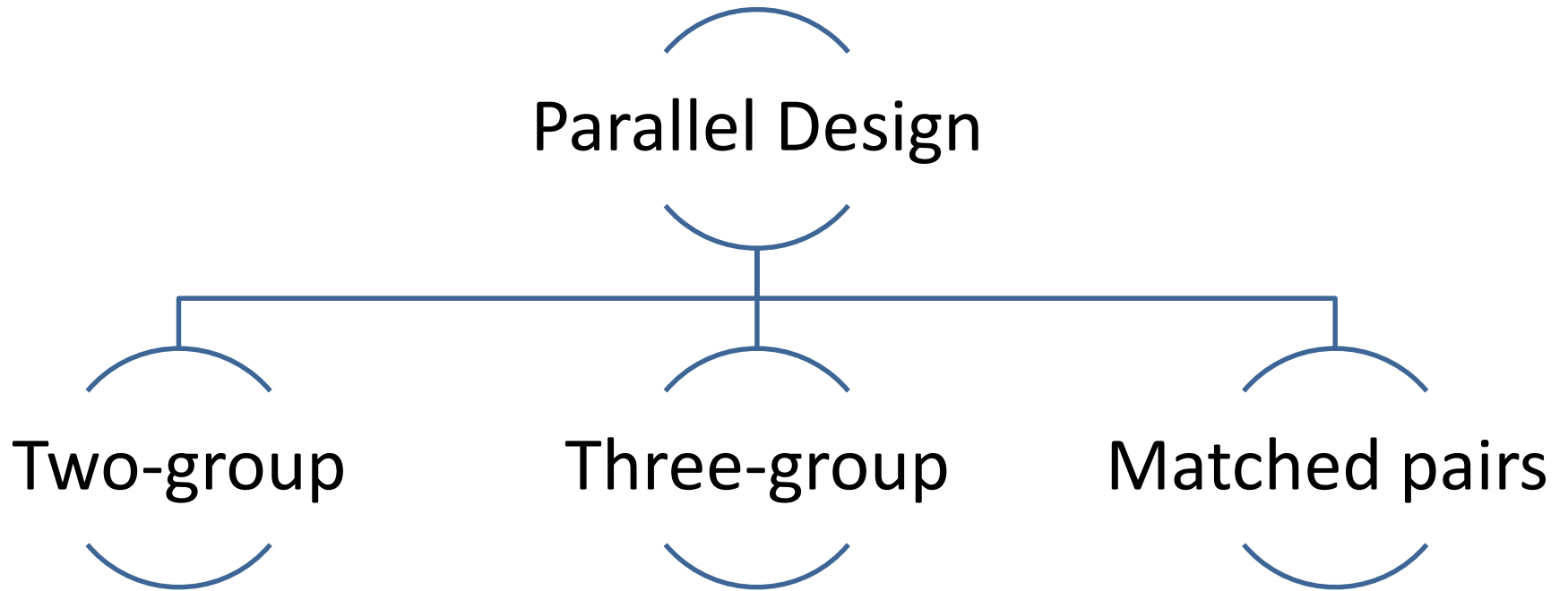
Parallel Design

❖ Disadvantages

❖ Inter-patient variability

- An appropriate design when the inter-patient variability is relatively small

Parallel Design



Parallel Design

❖ Two-group parallel design

- A treatment group
- A control group

❖ Three-group parallel design

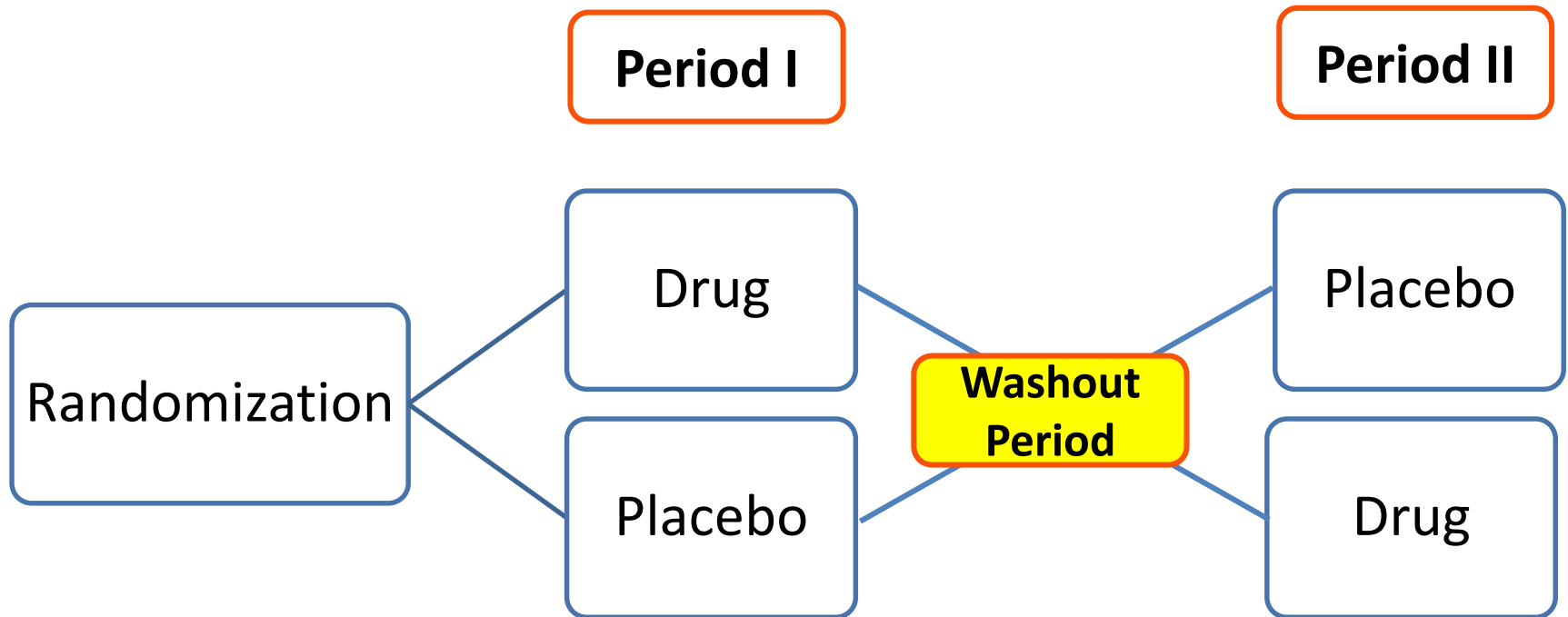
- A treatment group (new treatment)
- An active control group A (conventional treatment)
- A passive control group B (placebo)

Parallel Design

❖ Matched pairs parallel design

- A randomized complete block design with a block size of 2 in which each patient is matched with another of similar prognostic characteristics (e.g., age, sex, severity)
- One patient in each pair is assigned to the treatment and the other one to the control
- When the number of covariates is large, the matched pairs design is difficult to implement

Crossover Design



Inter- versus Intra-patient Variability

❖ Inter-patient variability

➤ Harm to parallel design

❖ Intra-patient variability

➤ Harm to crossover design

❖ The smaller the variability, the more accurate and reliable the clinical results will be.

Crossover Design

❖ Advantage

- It allows within-patients comparisons of treatments
- It removes inter-patient variability
 - Each patient is his/her own control
- It provides the best unbiased estimates for the differences between treatments
- It decreases number of patients needed

Crossover Design

❖ Disadvantages

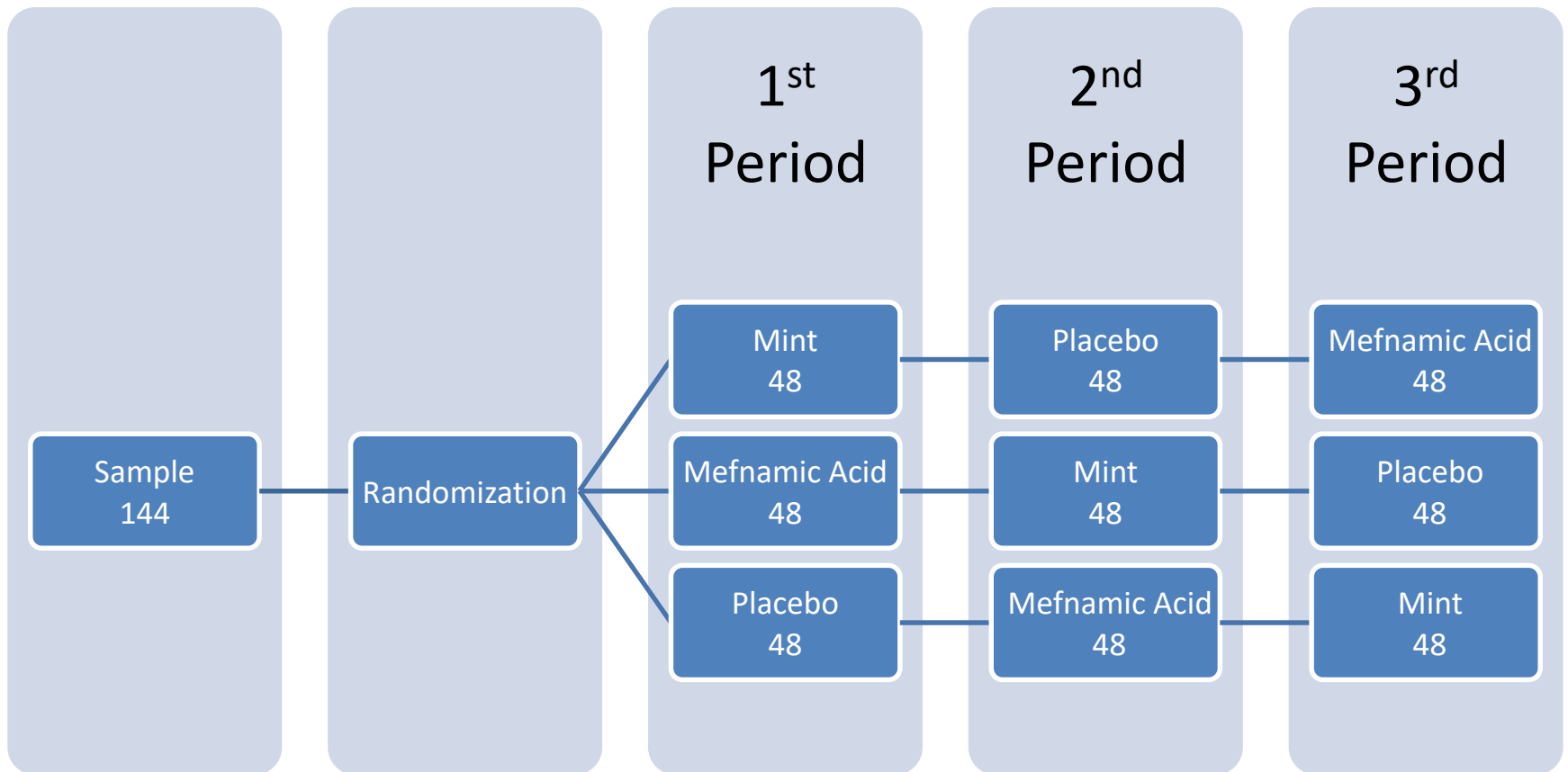
- It is applicable for:
 - Chronic and relatively stable diseases
 - Drugs with relatively short half life
 - Relatively short treatment periods
 - Baseline and washout periods are feasible
- It increases the duration of the study
- Its analysis is not straightforward
 - » The paired design
 - » The period and carry-over effects
- The effect of loss to follow-up

Crossover Design

❖ Washout period

- The washout (rest) period must be long enough for the treatment effect to wear off so that there is no carryover (residual) effect from one treatment to the next.
- No carryover effect is an assumption

Crossover Design



Factorial Design

		Treatment B	
		+	-
Treatment A	+	AB	AO
	-	BO	OO

Factorial Design

❖ Advantages

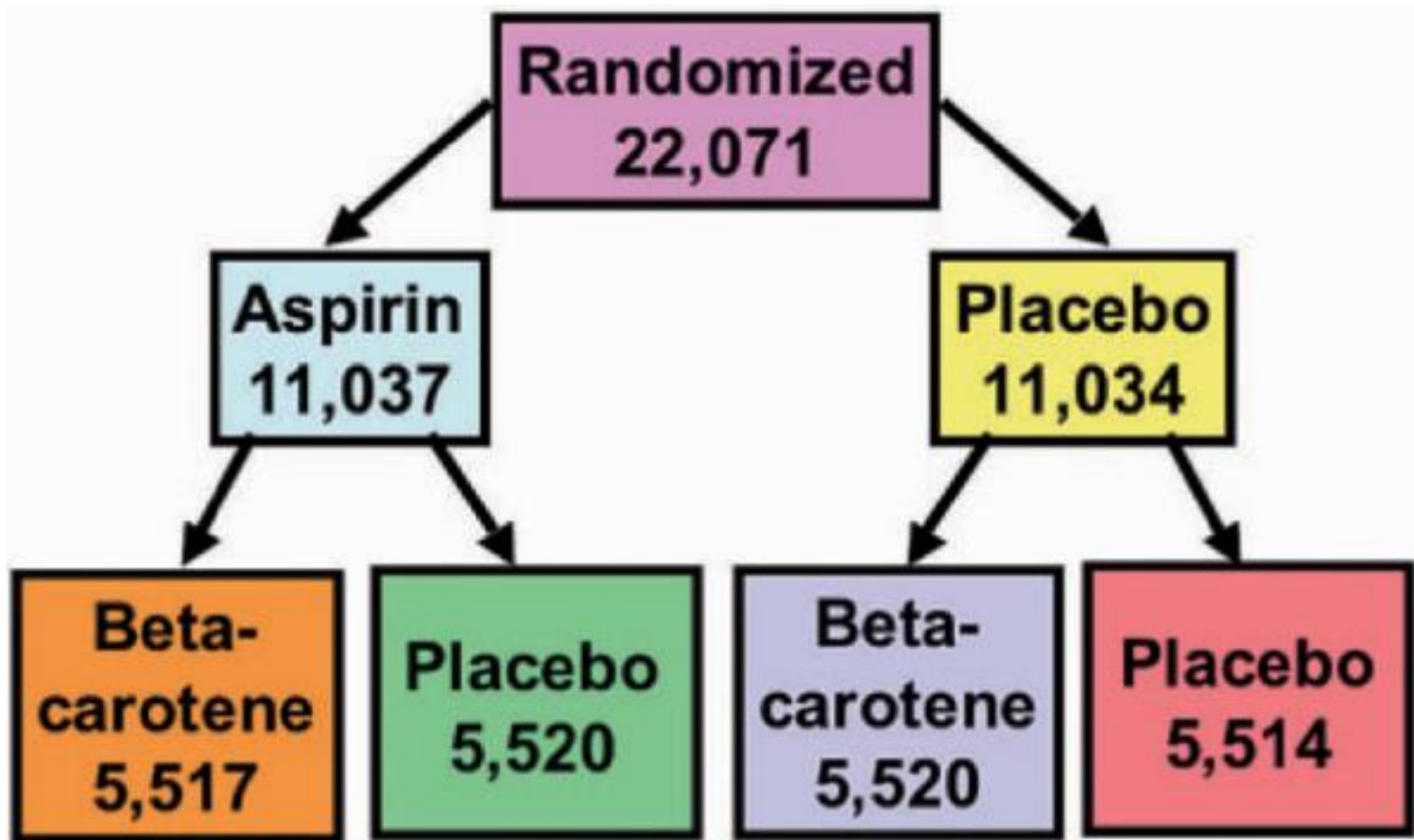
- One trial for assessing two treatment effect
- Discover the interaction between the two treatments
- Opportunistic situations

❖ Disadvantages

- Presence of both diseases simultaneously
- No interaction between A and B
 - » Synergistic effect
 - » Antagonistic effect

Factorial design



Aspirin → Cardiovascular & beta-carotene → Cancer





Factorial design

Aspirin → Cardiovascular & beta-carotene → Cancer

		Aspirin	
		+	-
Beta-carotene	+	Both aspirin and Beta-carotene (cell a)	Beta-carotene only (cell b)
	-	Aspirin only (cell c)	Neither Aspirin nor Beta-carotene (cell d)

-  Aspirin (cell a + cell c)
-  No aspirin (cell b + cell d)

		Aspirin	
		+	-
Beta-carotene	+	Both aspirin and Beta-carotene (cell a)	Beta-carotene only (cell b)
	-	Aspirin only (cell c)	Neither Aspirin nor Beta-carotene (cell d)

-  Beta-carotene (cell a + cell b)
-  No Beta-carotene (cell c + cell d)

Clustered Randomized Design



Clustered Randomized Design

❖ Clusters are units of trial

- Family
- School
- Worksites
- Athletic teams
- Hospitals
- Communities

Clustered Randomized Design

❖ Clustered (group) randomized design

- Nontherapeutic interventions
- Randomization at the cluster level
- Analysis at the cluster level
- Statistical inference at the cluster level

❖ Clinical trials

- Therapeutic interventions
- Randomization at the subject level
- Analysis at the subject level
- Statistical inference at the subject level

Clustered Randomized Design

❖ Nontherapeutic interventions

- A lifestyle intervention for increasing physical activity
- An educational program for smoking cessation
- Fluoridation of water

Clustered Randomized Designs

❖ Advantages

- Feasibility
- Cost benefit
- Avoid experimental contamination (important)
- Allow mass intervention → Public Health Trial

❖ Disadvantages

- Effective sample size is less than number of subjects
- Many units must participate to overcome unit-to-unit variation → requires larger sample size

Multicenter Trials

❖ A single-study site

- Can improve the quality and reliability of the data collection and consequently the inference of the clinical results.
- However, it has its own limitations:
 - » Rarity of patients or endpoint (outcome)
 - » Long-term duration
 - » Limitation of resources
 - » less generalizability of the results
- These limitations justify conducting a multicenter trial.

Multicenter Trials

❖ A multicenter study

- It is a single study involving several study centers.
- The data collected from these centers are intended to be analyzed as a whole.
- At all centers, an identical study protocol is used.
- A center or site is considered a natural blocking or stratified variable.

Multicenter Trials

❖ Advantages

- Adequate number of participants
- Reasonable time span
- More representative (generalizability) of findings
- Cooperation of investigators with similar interests

Multicenter Trials

❖ Tests for heterogeneity

- Statistical tests for heterogeneity across centers should be provided.
 - » Treatment-by-center interaction
- The interaction should be considered in light of the sample sizes
- Any extreme or opposite results among centers should be noted and discussed.

Multicenter Trials

❖ Treatment-by-center interaction

- The larger number of centers, the more likely a significant treatment-by-center interaction to be observed.
- For a sample size of 100, there are several options:
 1. 20 centers with 5 patients
 2. 10 centers with 10 patients
 3. 5 centers with 20 patients
- The probability of interaction: $1 > 2 > 3$

❖ The rule of thumb

- The number of patients in each center should not be less than the number of centers

Multicenter Trials

❖ Quantitative interaction

- The treatment effects across centers have
 - » Different magnitudes
 - » Same directions
- This difference does not invalidate the analysis of pooling data across centers.

Multicenter Trials

❖ Qualitative interaction

- The treatment effects across centers have
 - » Different magnitudes
 - » Different directions
- Thus, the overall or average summary statistics may be misleading and hence considered inadequate.
- In this case, it is preferable to describe the nature of the interaction and to indicate which centers contribute toward the interaction.

Multicenter Trials

❖ Imbalance sample size

- If there are too many centers, big imbalances among centers may occur.
- Some centers may have a few patients and others a large number of patients.

❖ Two combination approaches

- To combine these small centers to form a new center based on their geographical locations or other characteristics.
- To randomly assign the patients in these small centers to those larger centers.

THANK YOU