

Randomization & Blinding

Design and Analysis of Clinical Trials Concepts &
Methodologies
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Introduction

- ❖ Randomization is usually used
 - To control selection bias
 - To generate comparable groups
 - Free of confounding
 - Known and unknown
 - To enable valid statistical tests

Introduction

Random allocation

Random sampling



Randomization vs Random Sampling

Random allocation

- Critical for clinical trial
- Increase internal validity
- Comparability

Random sampling

- Critical for observational studies
- Increase external validity
- Generalizability

Introduction

❖ Random Sampling

- Not necessary per se
- Necessary for generalizability

❖ Random allocations

- Necessary for unbiased inference

Introduction

❖ Concealment

- Masking randomization process by using an unpredictable mechanism so that no one can foresee the allocation prior to assignment

❖ Qualified patient

- meets the inclusion and exclusion criteria
- has signed the informed consent form

Types of Randomization

❖ Complete randomization

1. The chance that a patient receives either the test drug or the placebo is 50%.
2. Random assignments are performed independently for each of the N patients.

Types of Randomization

Systematic randomization

Simple randomization

Block randomization

Stratified randomization

Systematic Randomization

❖ Assignment of patients to groups according to

➤ The order of enrollment

➤ every other patient is assigned to one group

➤ The dates of enrollment

➤ The patient's initial

How?

➤ The patient's birthday

How?

Systematic Randomization

- ❖ The assignment of patients to treatments can be predicted without error.
- ❖ The investigators or patients may be aware of which treatment the patients receive.

Simple Randomization

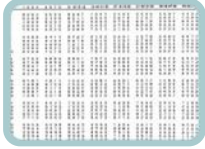


Table of random numbers



Computer random number generator

<https://www.randomizer.org/>



Coin tossing



Throwing dice



Drawing of lots



Shuffling cards or envelopes

Table of Random Numbers

32 44 44 82 77	59 82 09 61 63	64 65 42 58 43	41 14 54 28 20	03 99 11 04 61
88 57 07 40 15	25 70 49 10 35	01 75 51 47 50	48 96 83 86 03	38 55 59 55 54
95 16 03 92 21	22 30 49 03 14	72 87 71 73 34	39 28 30 41 49	17 54 67 37 04
80 58 04 18 67	17 71 05 96 21	06 55 40 78 50	73 95 07 55 52	32 46 35 28 61
60 47 80 33 43	25 85 25 89 05	57 21 63 96 18	49 85 69 93 26	69 57 26 87 77
95 04 35 26 80	45 78 05 64 87	09 97 15 94 81	37 00 62 21 86	24 12 26 65 91
45 54 77 08 18	59 84 99 61 69	61 45 92 16 47	67 41 71 71 98	61 19 63 02 31
31 73 25 72 60	47 67 00 76 54	45 37 62 53 66	94 74 64 95 80	30 53 22 17 04
85 99 59 03 07	54 30 47 18 03	26 82 50 55 11	12 45 99 13 14	03 78 89 75 99
35 84 18 57 71	08 10 55 99 87	87 11 22 14 76	14 71 37 11 81	48 22 85 33 79
85 30 18 89 77	29 49 06 97 14	73 03 54 12 07	74 69 90 93 10	60 36 39 45 53
54 06 61 52 43	47 72 45 67 33	47 43 14 39 05	31 04 85 66 99	83 79 94 24 02
98 52 52 43 35	24 43 22 48 96	73 27 75 88 84	11 45 61 60 82	32 95 00 76 05
90 39 16 11 05	57 41 10 63 68	53 85 63 07 43	08 67 08 47 41	19 32 25 38 45
26 62 91 90 87	24 47 28 87 79	30 54 02 78 86	61 73 27 54 54	11 22 09 47 47
37 30 14 26 78	45 99 04 32 42	17 37 45 20 03	70 70 77 02 14	31 75 15 72 60
92 00 39 80 85	76 66 87 32 09	59 20 21 19 73	02 90 23 32 50	88 49 29 93 82
16 45 39 45 14	39 01 49 70 66	83 01 20 98 32	25 57 17 76 28	30 93 44 77 44
99 83 70 05 82	81 23 24 49 87	09 50 49 64 12	90 19 37 55 68	22 88 84 88 93
07 36 29 77 03	76 44 74 25 37	98 52 49 78 31	65 70 40 55 14	78 21 21 69 93

Simple Randomization

❖ Complete

- The chance of allocation for each patient is 50%
- Randomization is performed independently for each of the N patients

❖ Limitations

- Imbalance which is a function of sample size

Simple Randomization

- ❖ When an equal number of patients are enrolled in each treatment group, the maximum statistical power for detection of the treatment difference is achieved.
- ❖ Statistical power
 - Small P-value
 - Narrow confidence interval

Balance Sample Size

Exposure	Cases	Controls	
+	40	20	OR = 2.67
-	60	80	95% CI: 1.36, 5.31
Total	100	100	P value = 0.002
+	20	30	OR = 2.67
-	30	120	95% CI: 1.25, 5.62
Total	50	150	P value: 0.005
+	4	38	OR = 2.67
-	6	152	95% CI: 0.52, 11.8
Total	10	190	P value: 0.130

Block Randomization

- ❖ One of the major disadvantages of simple randomization is the treatment imbalance
- ❖ Block Randomization
 - First, divide the whole series of patients who are to enroll in the trial into several blocks with equal or unequal lengths
 - Second, randomize the patients within each block

Block Randomization

There are three drugs (A, B, C) administered in each one of 9 blocks

No.	Drug	No.	Drug	No.	Drug	No.	Drug	No.	Drug	No.	Drug
1	B	10	A	19	C	28	B	37	A	46	C
2	A	11	B	20	A	29	A	38	C	47	A
3	C	12	C	21	B	30	C	39	B	48	B
4	C	13	B	22	A	31	C	40	B	49	B
5	B	14	A	23	C	32	A	41	C	50	C
6	A	15	C	24	B	33	B	42	A	51	A
7	C	16	C	25	C	34	B	43	C	52	C
8	B	17	A	26	A	35	C	44	B	53	B
9	A	18	B	27	B	36	A	45	A	54	A

Block Randomization

At most 1 difference in the samples of two groups

A	B	B	A	A	B	B	A	A	B	B	A	A	B	B	A
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16

At most 2 differences in the samples of two groups

A	A	B	B	B	B	A	A	A	B	A	B	B	A	B	A
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16

At most 3 differences in the samples of two groups

A	A	A	B	B	B	B	B	B	A	A	A	A	A	B	B
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
A	B	B	B	A	A	B	A	A	B	A	A	B	B	B	A
17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
B	B	A	A	A	B	A	B	A	B	B	A	B	A	B	A
33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48

Block Randomization

❖ Advantages

- Forced periodic balance
- Assurance of treatment balance

❖ Disadvantages

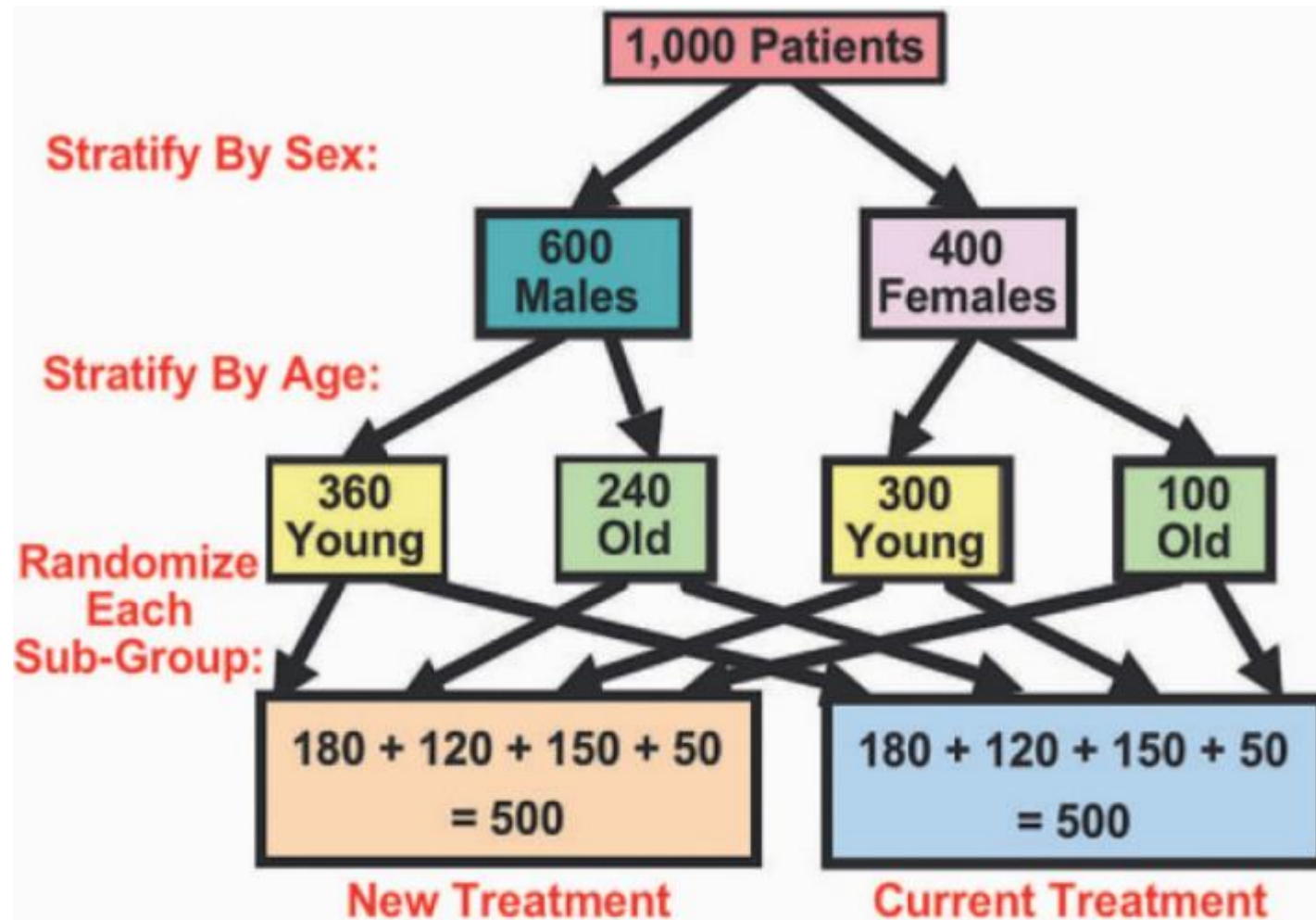
- When the block size is not blinded, the probability of correctly guessing the treatment increase at the end of each successive block.
 - Selection bias

Stratified Randomization

- ❖ If a covariate is known to be the cause of heterogeneity
- ❖ Then the patients are stratified or blocked into several homogeneous groups (or strata) with respect to the covariate
- ❖ Randomization of patients to the treatment is then performed independently within the strata

Stratified Randomization

The two groups become comparable in terms of sex and age



Stratified Randomization

- ❖ The idea of stratification is to keep the variability of patients
 - within-strata as small as possible and
 - between-strata variability as large as possible
- ❖ Stratification prevents imbalance with respect to important covariates.
 - The extreme case of stratification is the technique of matching.

Blinding

❖ Blinding also known as “masking”

❖ Blinding

➤ Being unaware of the treatment assignment

❖ Prevents information bias

➤ Observer bias

■ Assessment of outcome

➤ Patients bias

■ Patient’s psychological reaction

■ Behavior of patient

Blindning

❖ Open label

- No one

❖ Single blinded

- Either patients or investigators only

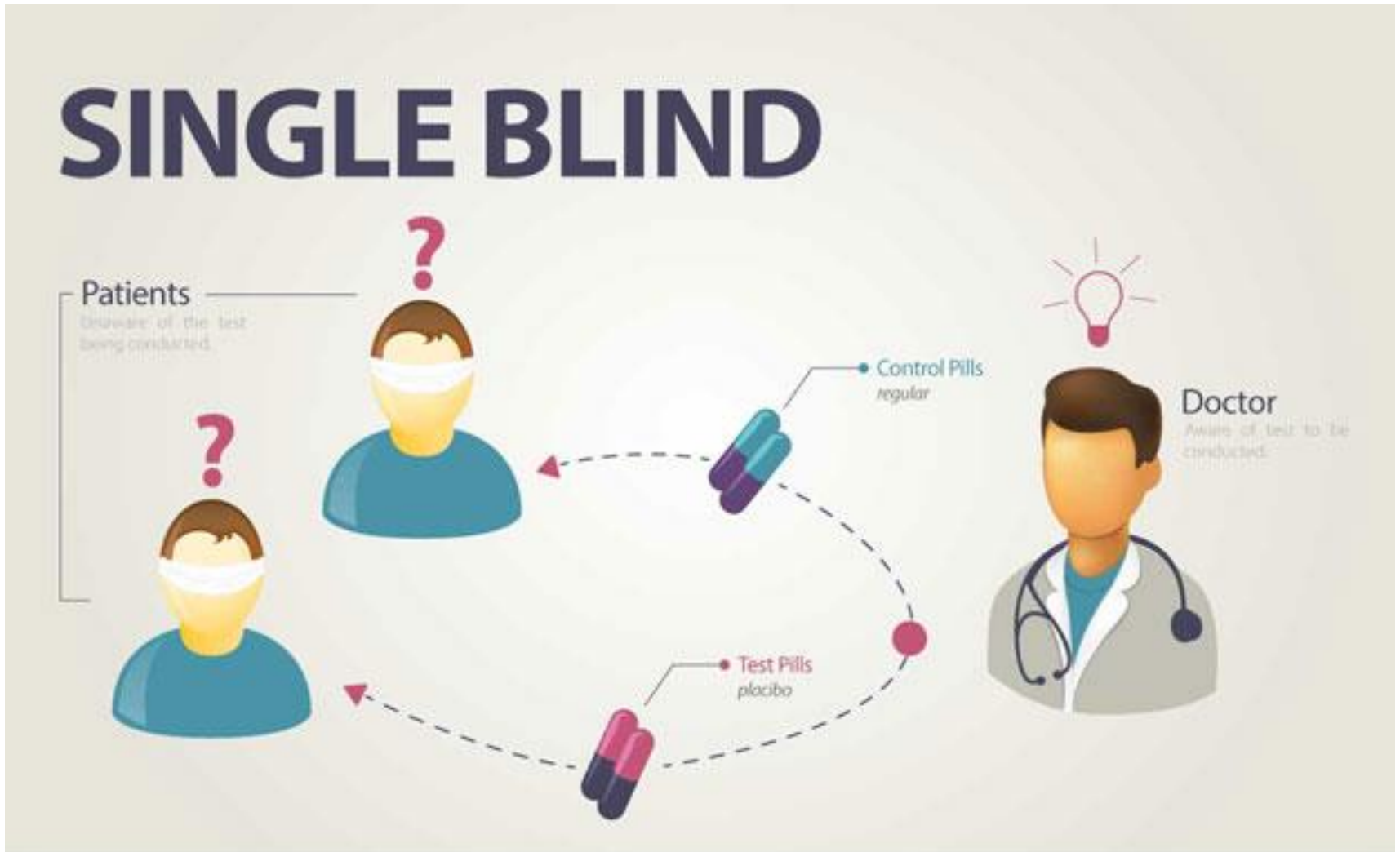
❖ Double blinded

- Both patients and investigators (who will monitor the outcome)

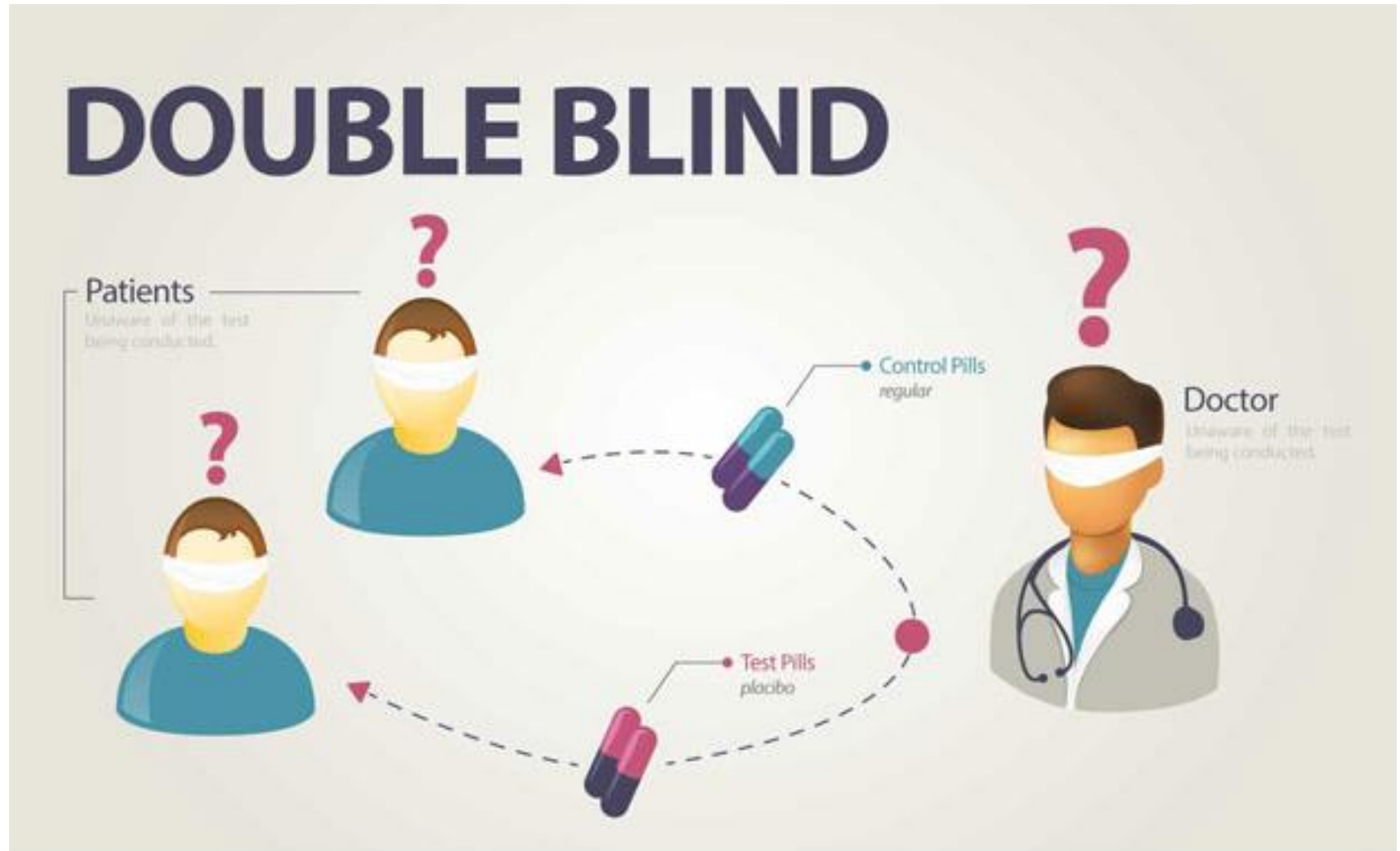
❖ Triple blinded

- Patients, investigators, analyzer

Blindning



Blindning



THANK YOU