

Evaluation :- Experiment → positive effective → max<sup>m</sup>  
 (side-effect → min<sup>m</sup>)  
 of treatment

US-FDA - Food, Drug, Administration

Weight loose  $80 \rightarrow 60$  <sup>min</sup> side effect →  
 Cost-optimization - Cost benefit  
 cost-eco  
 Radiations - Genes  $\Rightarrow$  pharmacogenomics } ✓

## Evaluation

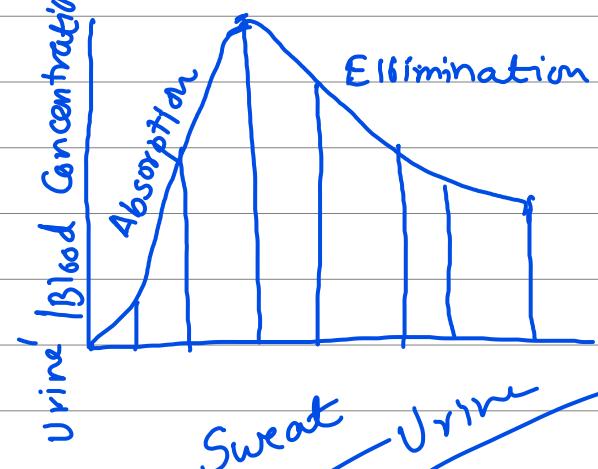
## Pharmacology

### pharmacodynamics

Dr.s.  
Clinicians  
Drugs impact body  
Drug administered  
headache gone

### pharmacokinetics

body's impact drug



Spilker's Defn

Clinical Trial subset

(Trials Phase-I

II

III

Piantadosi  $\rightarrow$  Humans  
Clinical Research  $\rightarrow$   $x \rightarrow$  drug  $\rightarrow$   $y_x$  disease.

Pharma CRO Clinical Research Organizations

Co.

/ state Health Dept / CRI

preclinical trials  $\leftarrow$  Animals  $\rightarrow$  I

side effects

$P(\text{Death})$  Fund  $\rightarrow$   
 $\text{due to } x$   $\rightarrow$   $0.0001$

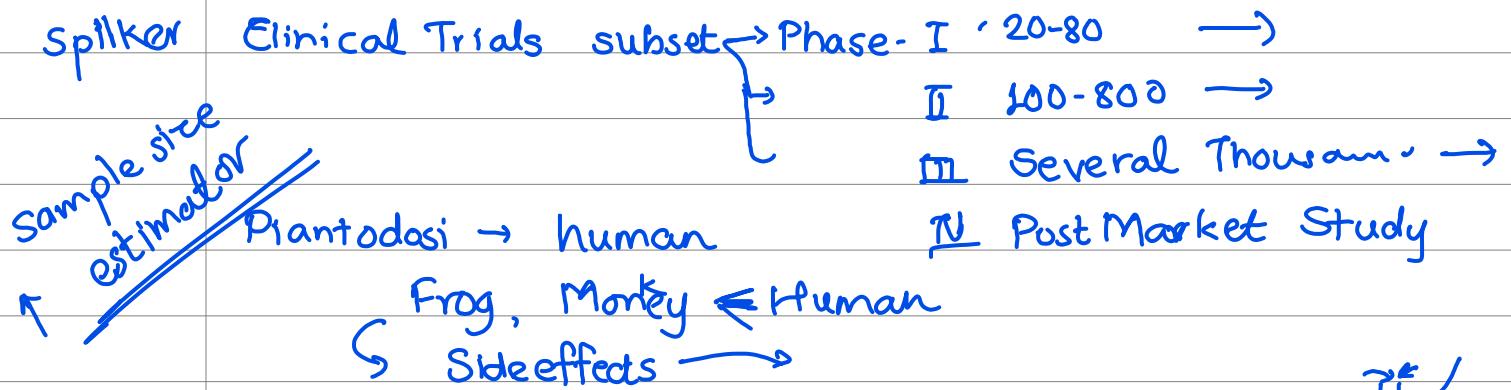
Phase-I  
Life threatening  
side effects

$\rightarrow 20/80 \rightarrow$  side effects min

$\rightarrow 800 - 1000 \rightarrow$  effectiveness side effect

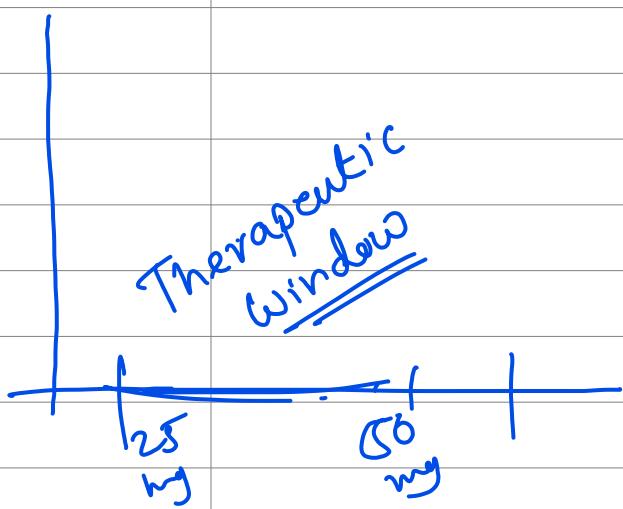
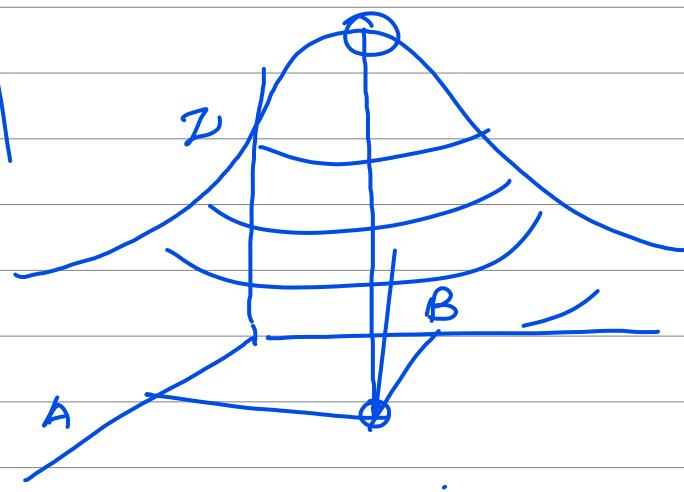
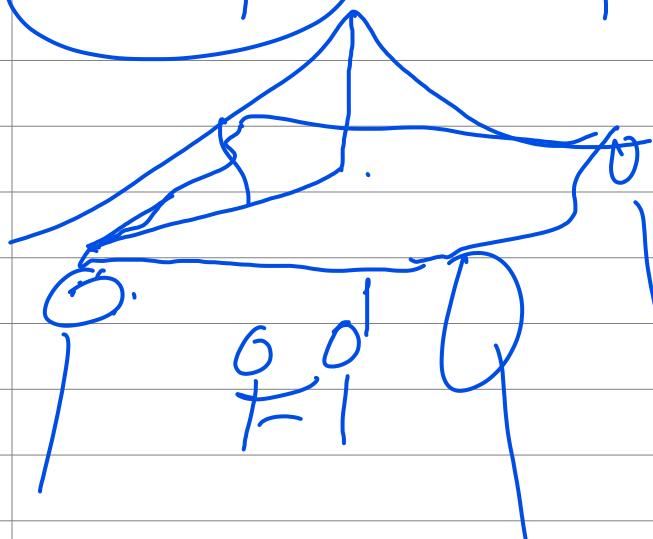
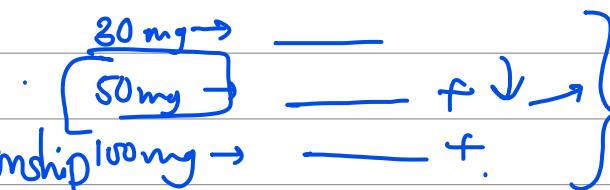
$\rightarrow$  Thousands  $\rightarrow$  Physicians labelling

$\rightarrow$  Post Market Analysis



Titration Design

Dose-Response Relationship



10mg  
50mg  
80mg

MED - Min<sup>m</sup> Effective Dose

MTD → Max<sup>m</sup> Tolerable Dose

0.00001

Life threatening side effect

Physicians label

$\mu_p$   
Placebo ~~(X)~~

- ✓ ②
- ✓ ③
- ✓ ④

$\mu_A$   
Active drug → ① Active Chemical effect  
~~(X)~~ { ② Environmental factor  
 ✓ ③ Body ← WBC/RBC  
 ✓ ④ Physiological

$\mu_A - \mu_p$  actual effect of that ingredient

Statistical difference

$C_p$  ?

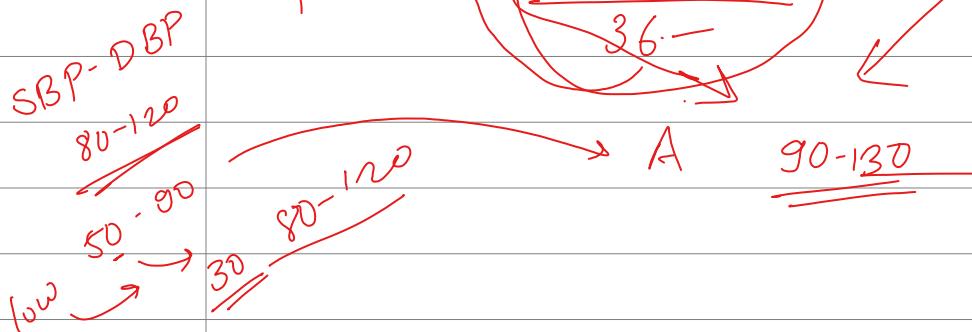
UST - LSL

36 -

Clinical diff

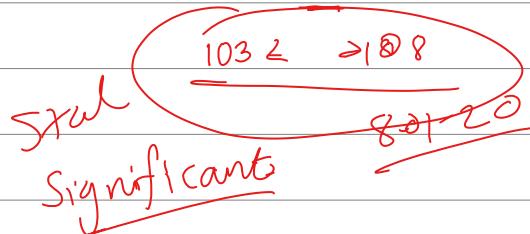
LSL ? USL ?

Clinician / Doctors



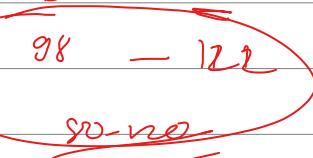
$$A \rightarrow \mu_A = 105$$

$$\delta_A = 1$$

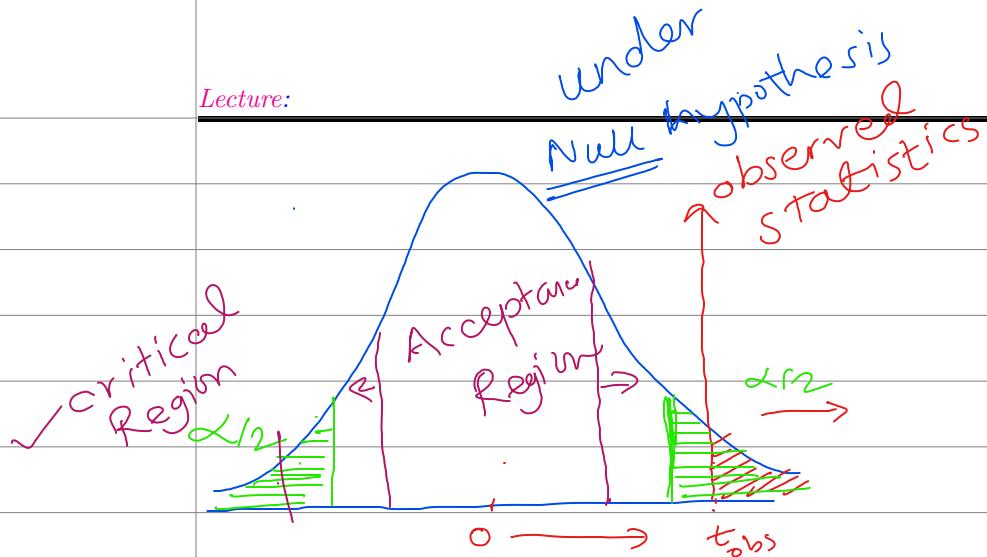


$$\beta = \mu_B = 110$$

$$\delta_B = 2$$



Clinician



Two way       $H_0 \Rightarrow \underline{\underline{\mu = \mu_0}} \Rightarrow 2(1 - \text{CDF})$

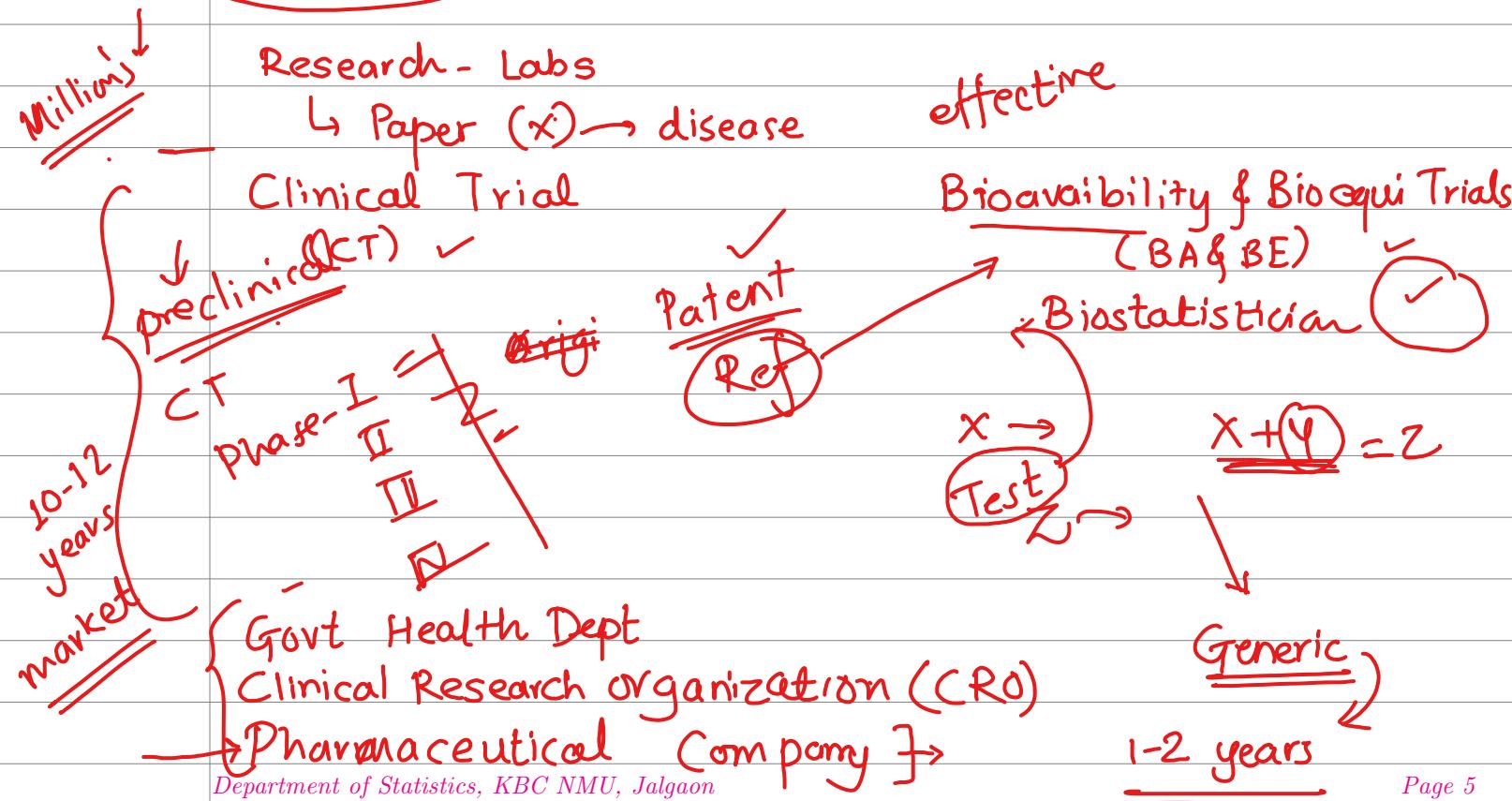
One way       $H_0 \vdash \underline{\underline{\mu \geq \mu_0}} \Rightarrow 1 - \text{CDF}$

$\underline{\underline{\mu < \mu_0}} \Rightarrow \text{CDF}$

*Confusion*  
*Rohan Sir*

Patent  
Trademark filed (Branded)  
Active ingredient (x)  
Inactive ingre

Generic Drug  
-Copied -  
→ same (x)  
→ different



BA - BE  
patent → generic

→ Same dosage  
Strength  
Safety  
Route of administration



Non comm IND

① Sponsors → Physician → Govt → NARI → CRO → TCR → Pharma Co.

② Market Research

③ ADA

Objective

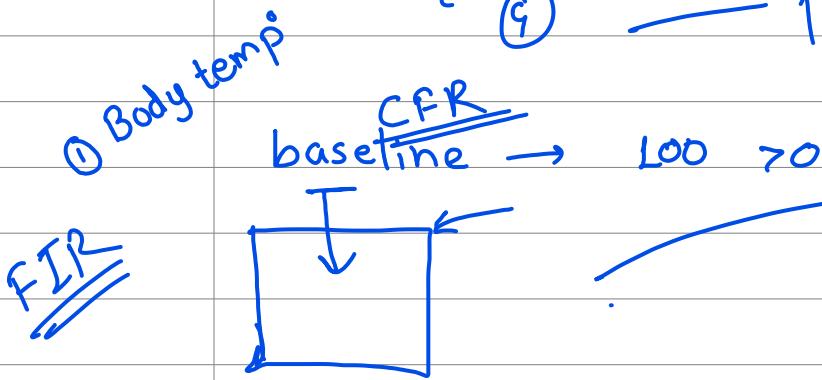
- ① Treatment to reduce weight
- ② Immunity
- ③ Muscles

Objectives

①	—	—	✓
②	—	—	✓
③	—	—	✓
④	—	—	—

Object

- ① Fever ↓
- ② Cold ↓
- ③ — ↓



effective or not  
clinical endpoint  
 $\leq 100$

## Hypothesis.

Lecture:

Manoj C Patil

$$\textcircled{1} \quad H_0: \mu_T > 100$$

$$H_1: \mu_T \leq 100$$

example

$$\textcircled{2} \quad \mu_A = \mu_B = \mu_C \quad H_1: \text{at least one treatment mean differs}$$

$$H_1: \mu_i \neq \mu_j \quad i \neq j$$

Inclusion & Exclusion

Inclusion & Exclusion for CTs

①  $< 18$  &  $\geq 60$  old age Exclude

② Feeding mother / pregnant

③ History disease

Medications

④ \_\_\_\_\_

⑤ \_\_\_\_\_

Inclusion  
Some

Disease.

Healthy volunteer

③  $> 18$

④ \_\_\_\_\_

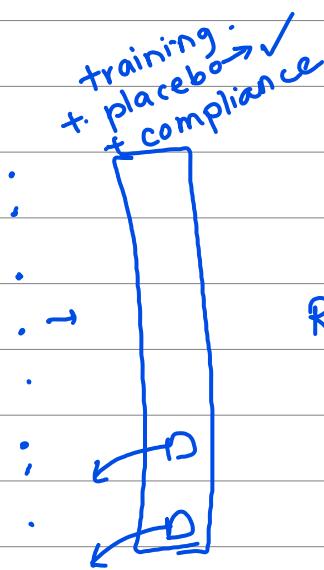
⑤ \_\_\_\_\_

Some inclusion & all exclusion criteria  
follow  
not followed

Run-in Period

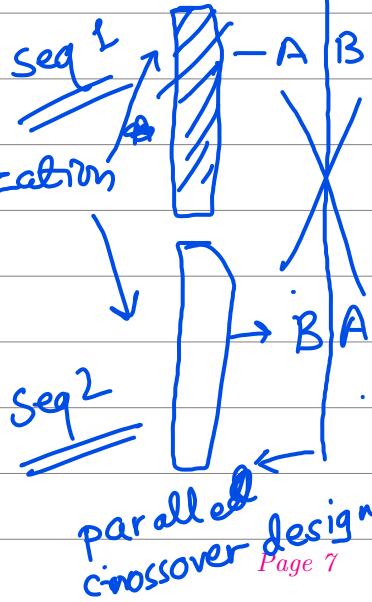
inclusion &  
exclusion  
criteria

Titration  
design



+ training  
+ placebo  
+ compliance

Randomization



parallel  
crossover design

?

Titration design - ①

②

③

④

⑤

⑥

Upward

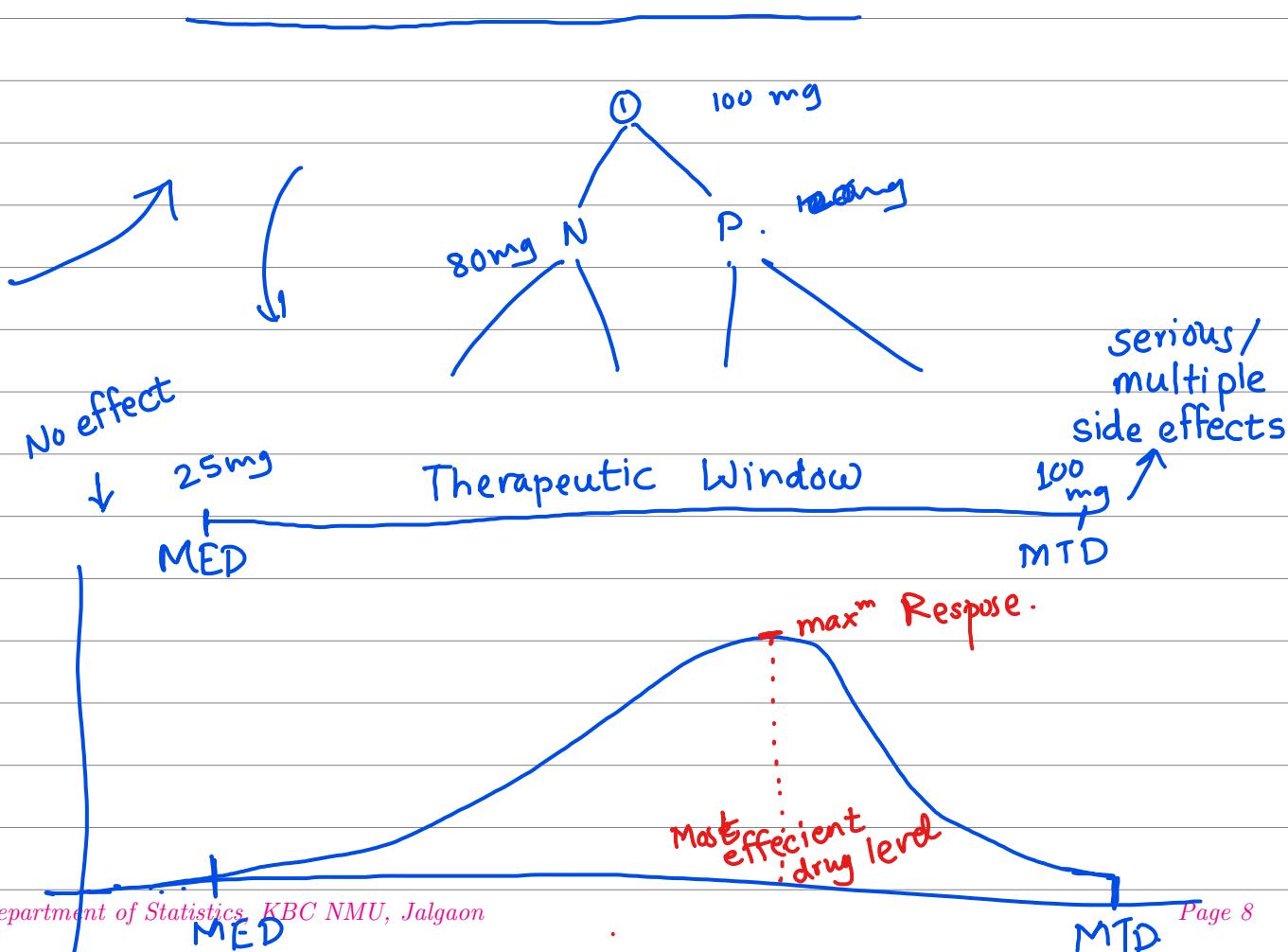
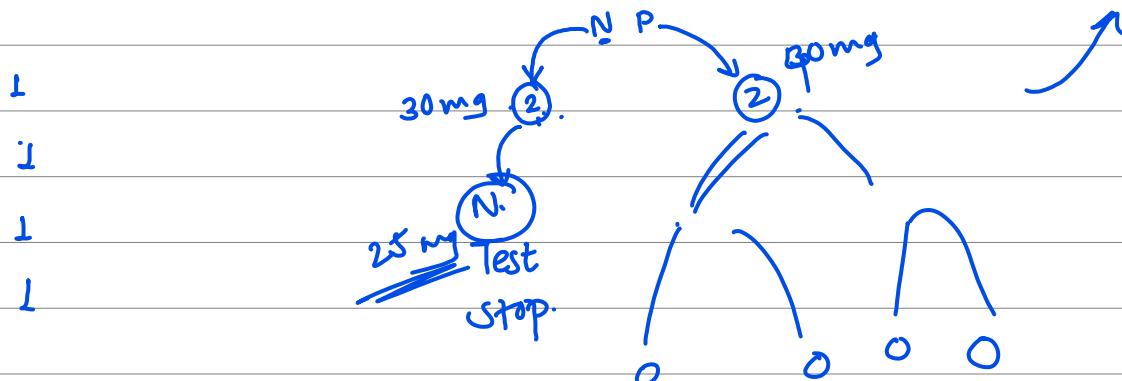
Upward-downward

downward

Human

Safety

① . 30mg -



## ① Methods of blinding

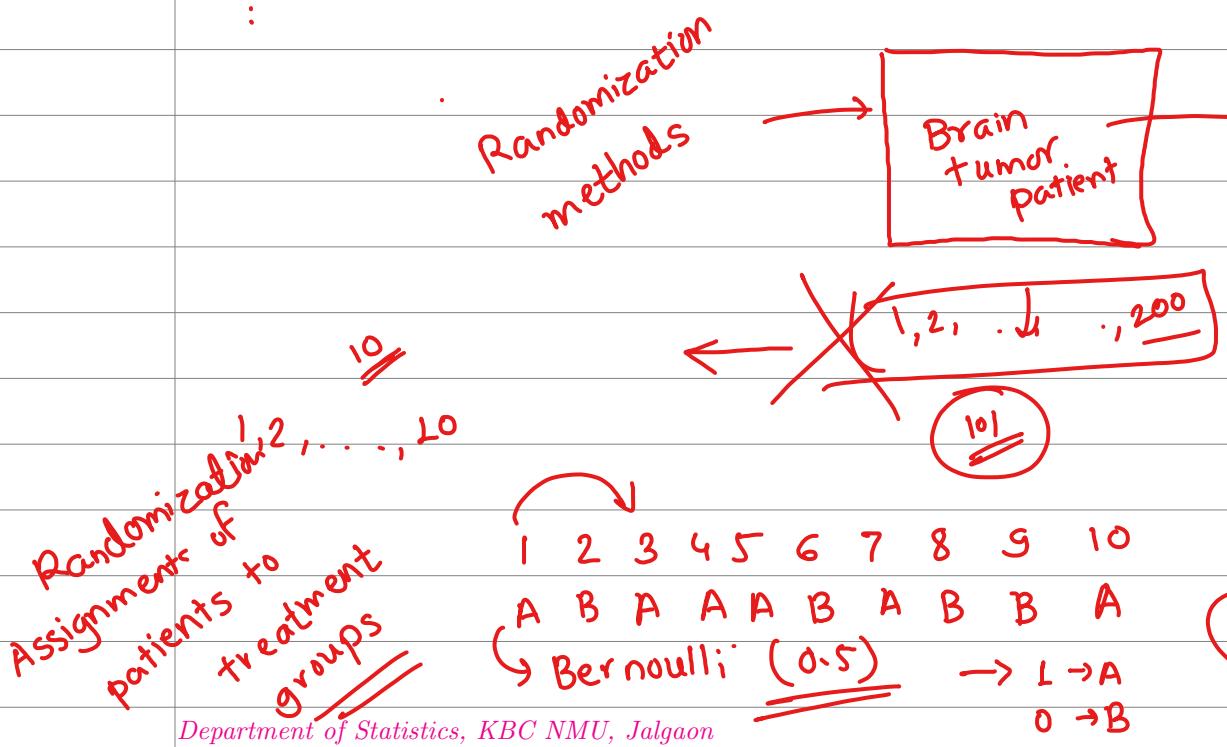
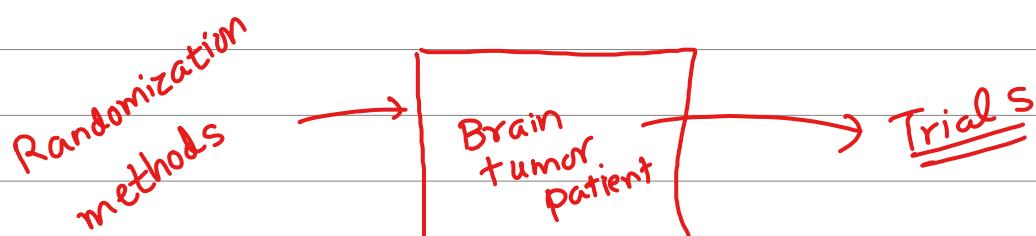
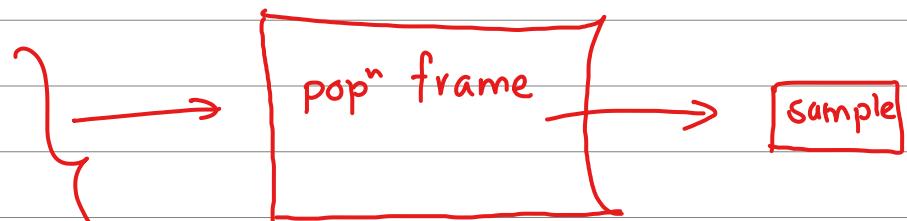
- open label** ① No - Everyone knows
- ② Single - Patient / Dr. any one is blinded
- ③ Double - & no one knows the allocations
- ④ Triple - Patient / Dr / Other staff all are blinded  
↳ Data collectors - Nurse

Data Analysts - Statisticians



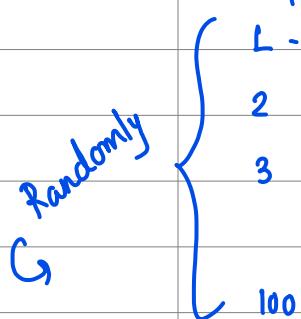
### \* Randomization ✓

- ① SRS w/R
- ② Stratified
- ③ Cluster
- ④ Systematic
- ⑤ Double Sampling



## ① Complete Randomization

drugs  
A & B assign with equal prob.

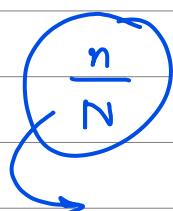


using R → SRSWR

① sample

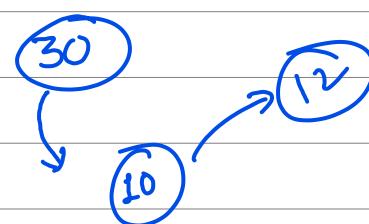
② Bernoulli: —  $0.5 \rightarrow L \rightarrow A$   
 $0 \rightarrow B$

③ Uniform  $0.5 < 1$       A  
                            B



Sample fraction

$$\frac{\min(n_A, n_{\text{placebo}})}{\text{total no. of patients}}$$



No. of individual      Risk ↓

A      B      C      Fair?

100      10

Sample fraction should be  $\frac{1}{n_D} \rightarrow \frac{1}{2}$

Randomization

100,000  
100 → Treatment

① Patient Popn → <sup>Random</sup> Sample drawn

Invoked popn

② Patient - Drug assignment

Group 1 - Active → 1, 3, ..., 7, 9, 21, 29

Group 2 - Placebo

Sample fraction = 0.5

1 2 3 4 5 6

(A A A B B B)

ABA BAB ✓

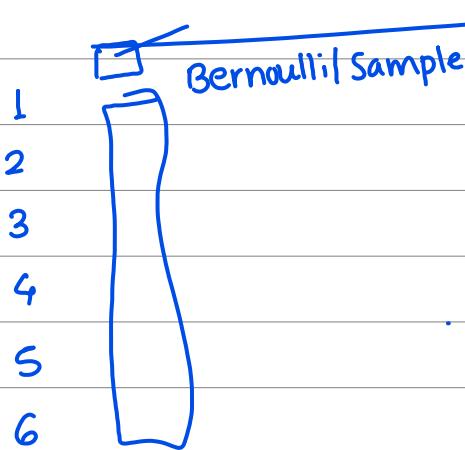
A 1 4 6 ✓       $n(A) = 3$

B 2 3 5 ✓       $n(B) = 3$

$(1 \ 2 \ 3 \ 4 \ 5 \ 6) \rightarrow$  Random Sample without replace  
A A A

3 2 5 ~~1~~, 4 6

A A B A B B



	A	B
1	A	A.
2	A	B.
3	A	B.
4	B	A.
5	B	A.
6	B	B

③

Forced

21	1	6	B
22	2	3	A.
23	3	2	A.
24	4	4.	B.
25	5	1	A.
26	6	5	B.

$\frac{1}{n_D}$  Sample fraction =  $\frac{1}{n_D}$

$1-3 \rightarrow A$   
 $4-6 \rightarrow B$

### \* Complete Randomization

$n_A$

$A \rightarrow D_1$   
 $B \rightarrow I_2$

out 20 patients ] not comparable group  
 $0.5 \quad 0.5$

$n_m \approx$

Balanced  $\Rightarrow$  10 sub A & B each comp

Imbalance  $\Rightarrow P[n_A \neq 10] = 1 - P(n_A = 10) = 1 - \frac{20}{C_{10}} 0.5^{20}$

$n_A \sim \text{Binomial Distribution}(20, 0.5)$

### \* Permutated block Randomization.

To avoid Treatment imbalance

Forcefully Treatment balance

30 patient divide in 3 blocks

1	10	B	11	1	21	1
2	2	A	12	2	22	2
3	3	B	13	3	23	3
4	4	B	14		24	
5	5	B	15		25	
6	6	A	16		26	
7	4	A				
8	1	A				
9	5	A				
10	10	B	20	10	30	10

$n_A \approx n_B$

$n \approx n/2$

$n_A = 10 \Rightarrow B = 10 \Rightarrow A = 10 \Rightarrow P = 10/20 = 0.5$

Permutation of 1: blocksize

Do this procedure for all blocks  $\rightarrow$  Then combine

$$\begin{cases} n_A = 5 \\ n_B = 5 \end{cases}$$

block size  $\rightarrow$

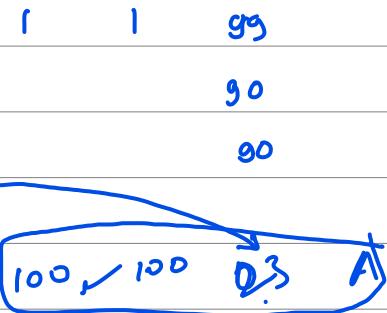
30 patients divided into 3 blocks

what if I want only 2 blocks

?	1	!	16	1	30 $\rightarrow$ 1
$n_A = 15$ $n_B = 15$	2	8-A	7-B		
		T-B			
	15	15	30	15	10

Suppose we have 99 no. of patients & two treatments  
 → Balance impossible  $\Rightarrow$  Create dummy patient ✓  
 $99 + 01 = 100$

*potential bias*



\* *I have used permuted block randomization here.*

			block 5
1	M	A	
2	F	B	
3	M	A	
4	F	B	
5	F	B	
6	M	A	
7	F	B	
8	M	A	
9	F	B	
10	M	A	

*Randomized* *Com* *Treatment* *balance* *(60)* *A.* *B.*  
*5 m M.* *5 o* *5 ←*

*perfect*

*comparable groups*

### Adaptive Randomizations

① Treatment Adaptive Randomization

② Covariate A R

(Stratified Randomization)

③ Response A R

