

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

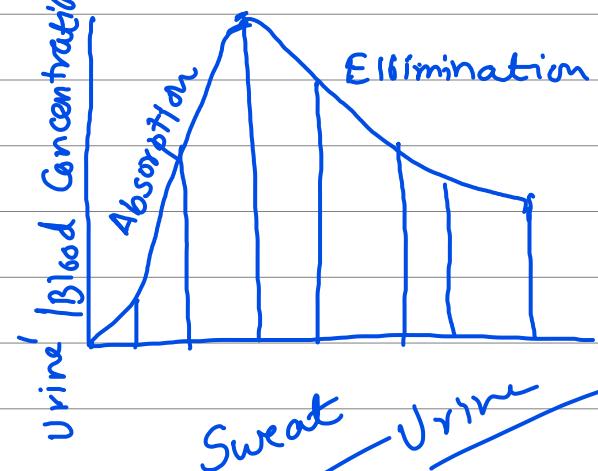
## Pharmacology

### 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

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

Phase-I

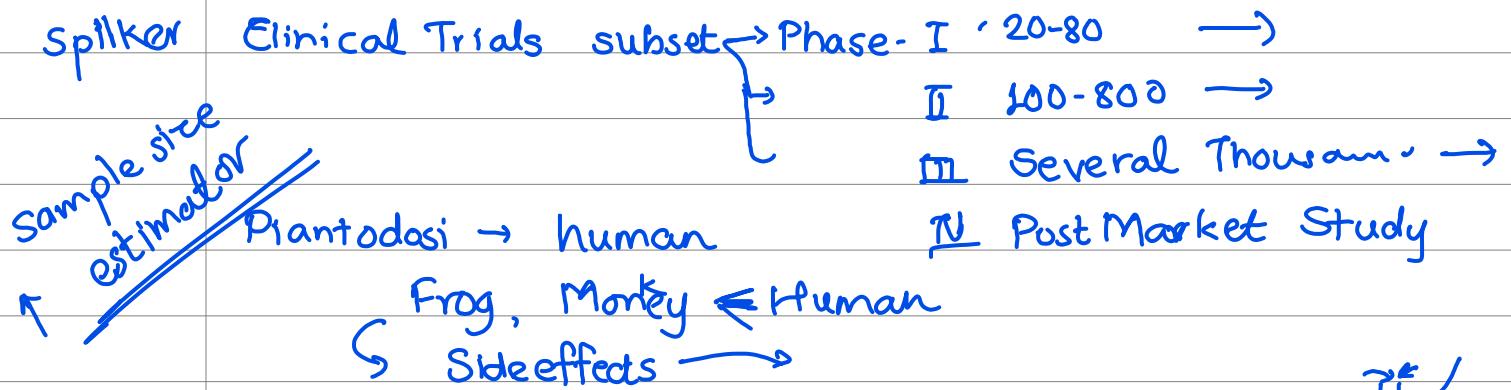
$\rightarrow$  20/80  $\rightarrow$  side effects min

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

$\rightarrow$  Thousands  $\rightarrow$  Physicians labelling

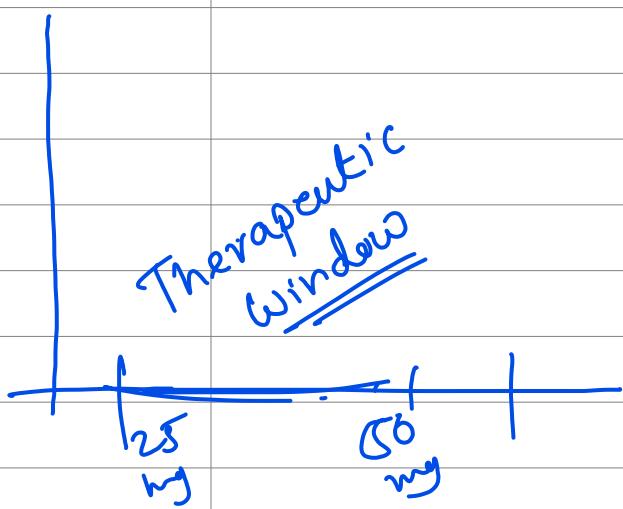
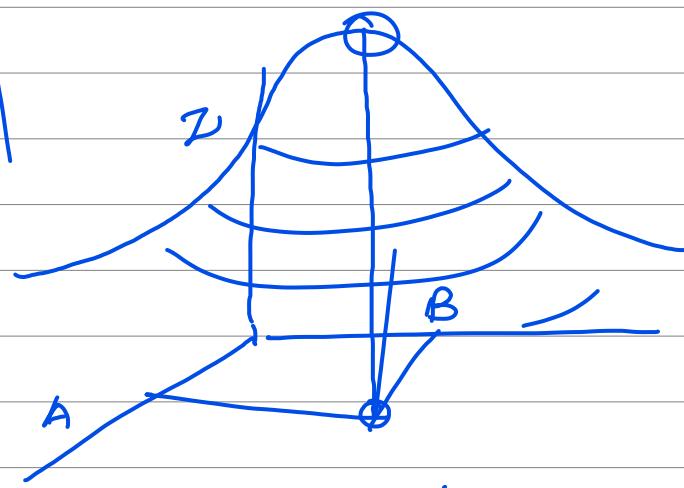
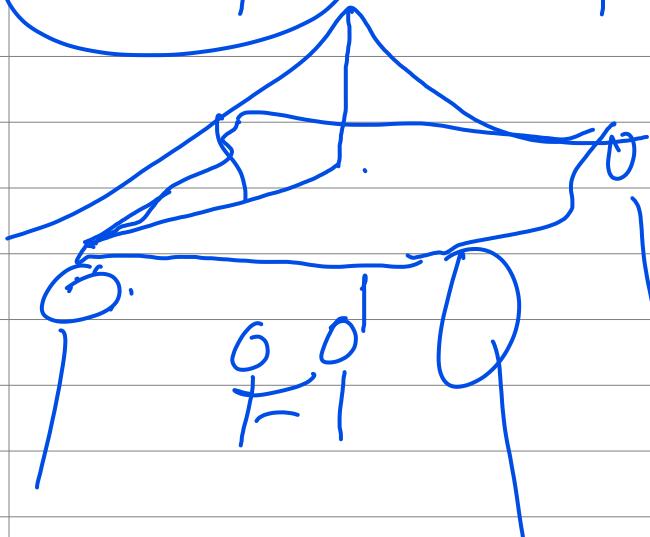
Life threatening side effects

= IV 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

$C_p$  ?

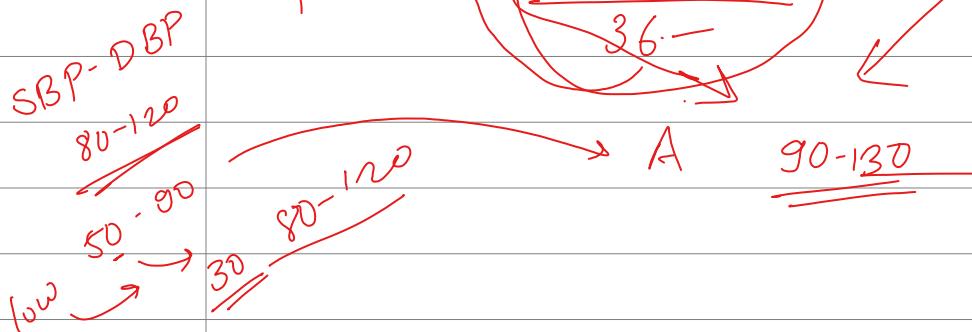
UST - LSL

36 -

Clinical diff

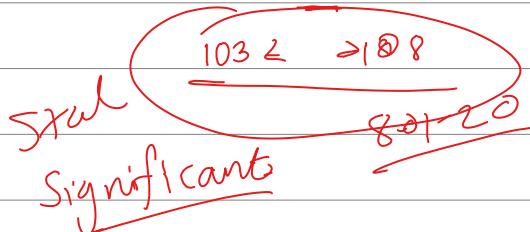
LSL ? USL ?

Clinician / Doctors



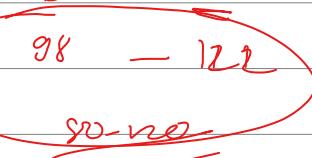
$$A \rightarrow \mu_A = 105$$

$$\delta_A = 1$$

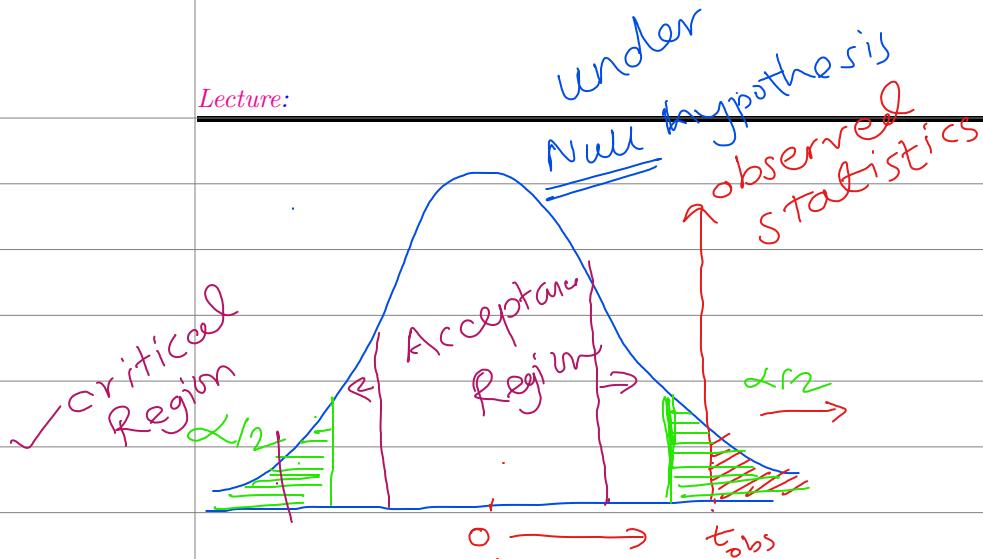


$$\beta = \mu_B = 110$$

$$\delta_B = 2$$



Clinician



$$\alpha > p$$

$p < \alpha \Rightarrow \text{Reject } H_0$

$p > \alpha \Rightarrow \text{fail to}$

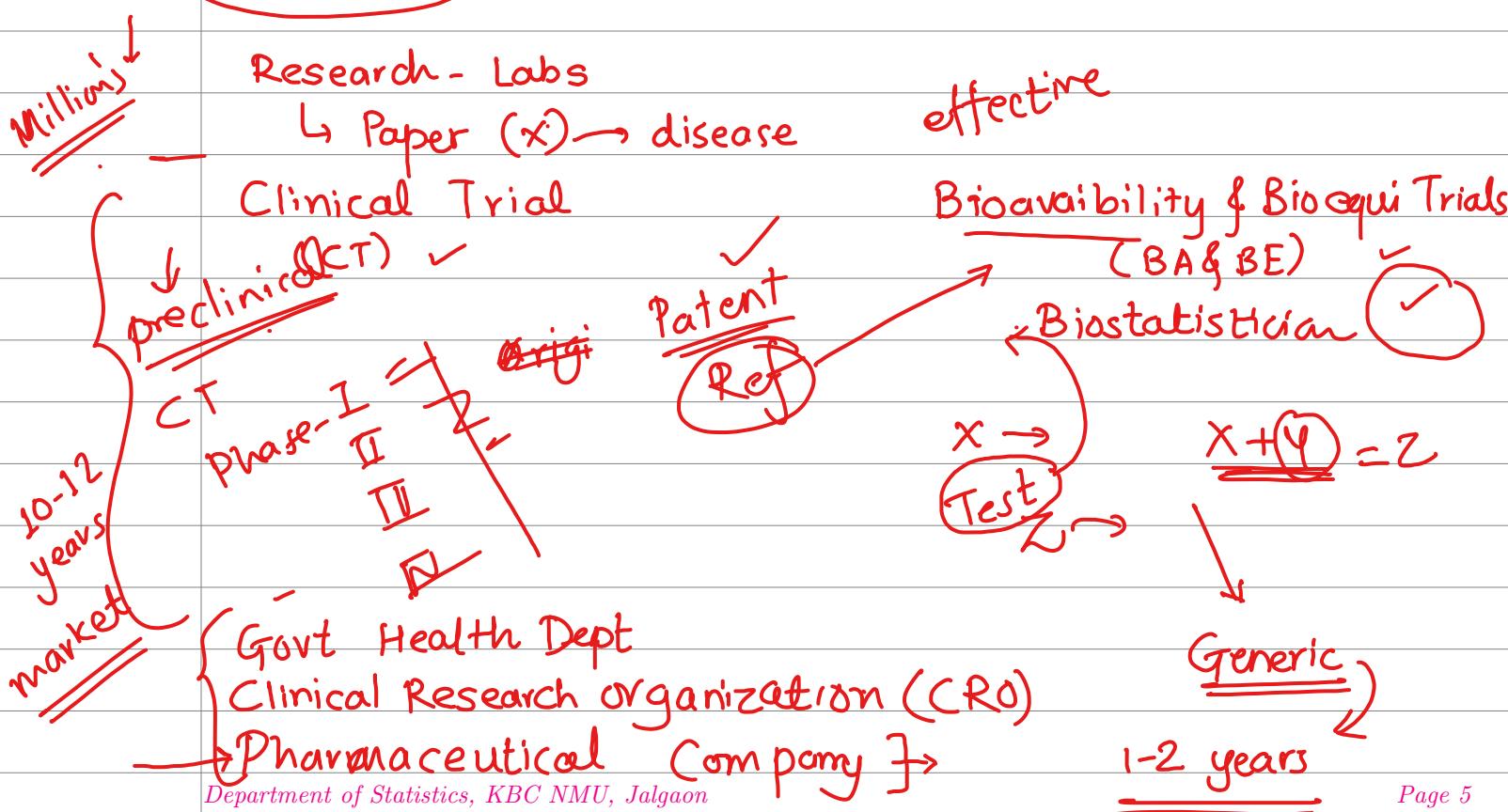
$\text{Reject } H_0$

~~Confusion~~  
~~Rohan Sir~~

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

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

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



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

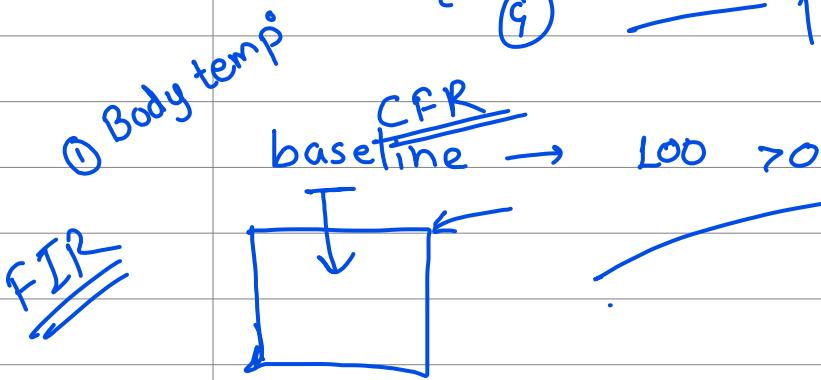
- ① Treatment to reduce weight
- ② Immunity
- ③ Muscles

Objectives

①	—	—	✓
②	—	—	✓
③	—	—	✓
④	—	—	—

Object

- ① Fever ↓
- ② Cold ↓
- ③ — ↓



effective or not  
clinical endpoint  
 $\leq 100$

## Hypothesis.

## Lecture:

*Manoj C Patil*

$$H_0: \mu_T > 100$$

$$H_1: \mu_T \leq 100$$

## example

$$\textcircled{2} \quad \mu_A = \mu_B = \mu_C$$

$H_0$ : at least one treatment mean  
 $H_1$ :  $\mu_i \neq \mu_j$  for some  $i \neq j$

## Inclusion & Exclusion for CTs

- ① < 18 & > 60 old age, Exclude

- ## ② Feeding mother / pregnant

- ③ History disease M.

- 4

- 

## Disease

## ② Healthy volunteer

③ 718

4

1

2

Some inclusion & all exclusion criteria  
follow  
not followed

## Run-in Period

*inclusion*  *exclusion* *criteria*

# Titration design

+ training ✓  
+ placebo ✓  
+ compliance ✓

# Randomizati

ation

Seq<sup>2</sup>

parallel crossover design  
Page 7

?

Titration design - ①

②

③

④

⑤

⑥

Upward

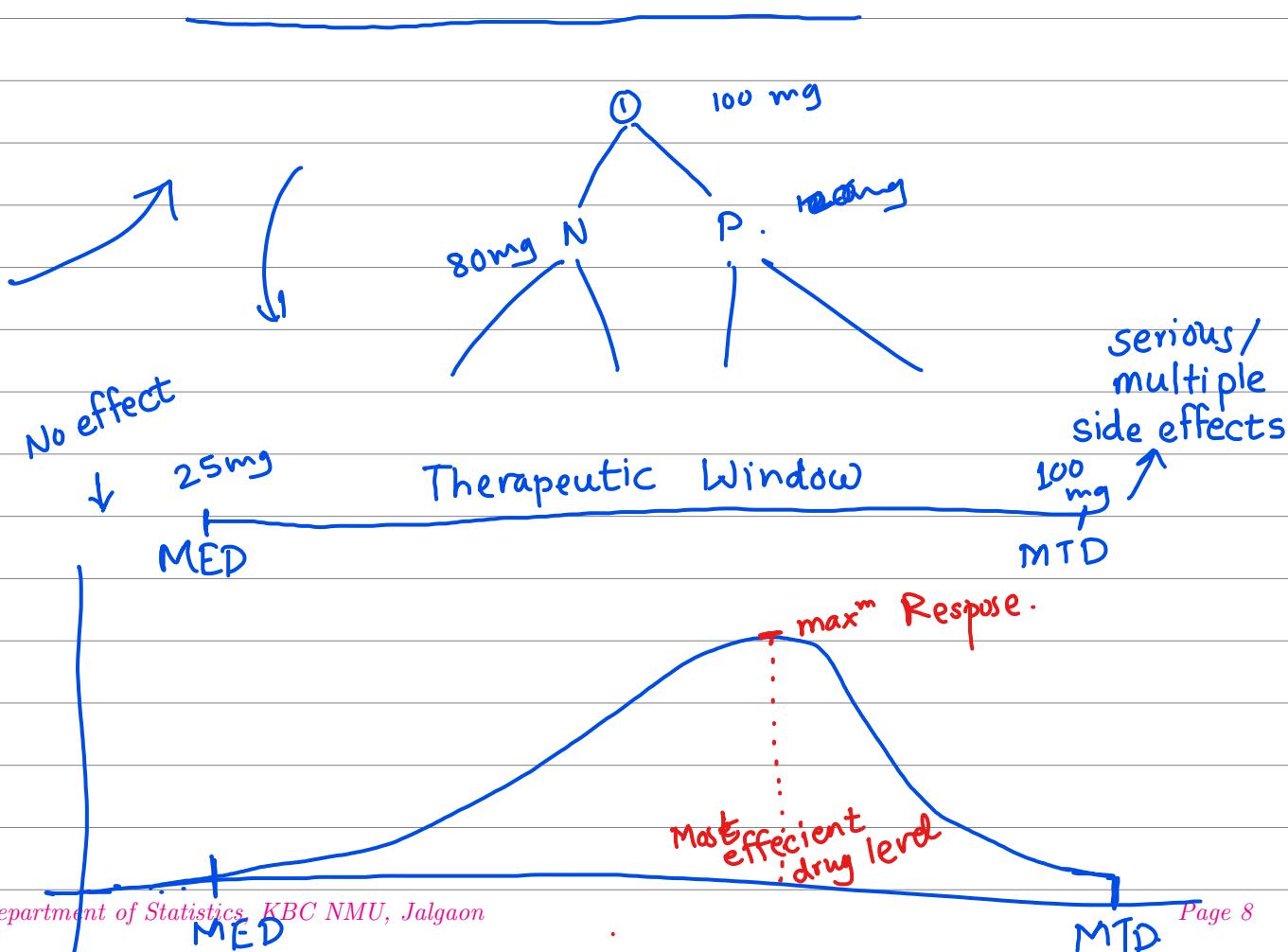
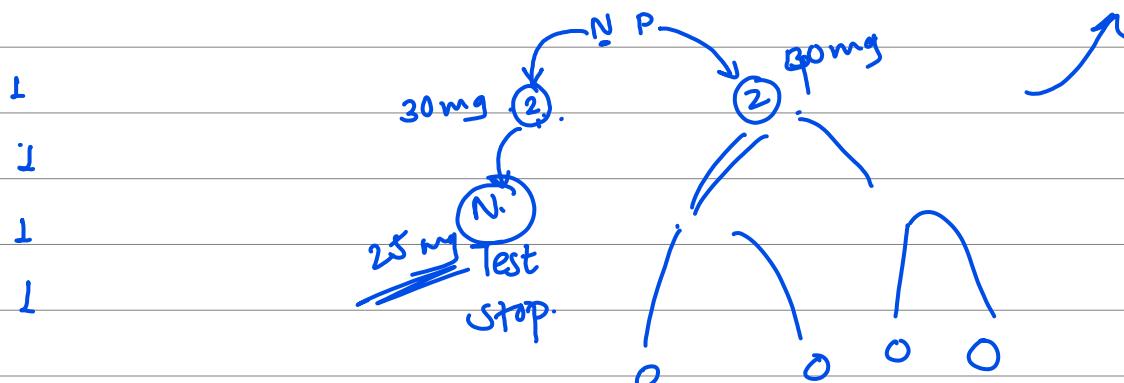
Upward-downward

downward

Human

Safety

① . 30mg -



## ① Methods of blinding

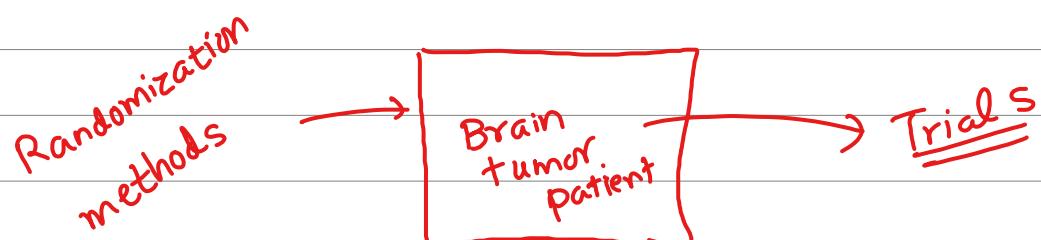
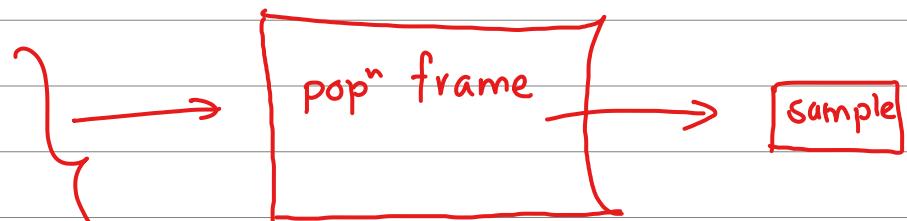
- open label** ① No - Everyone knows
- ② Single - Patient / Dr. any one is blinded
- ③ Double - & no one knows the allocations
- ④ Triple - Patient / Dr / Other staff all are blinded  
↳ Data collectors - Nurse

Data Analysts - Statisticians

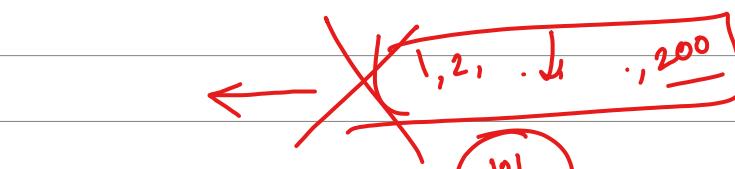


### \* Randomization ✓

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



Randomization  
Assignment of patients to treatment groups

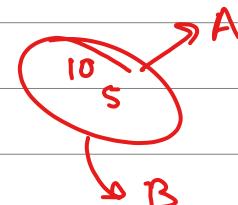


Randomization  
Assignment of patients to treatment groups

Bernoulli ( $0.5$ )

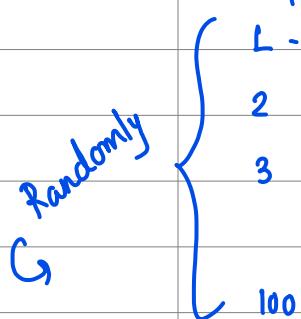
1	2	3	4	5	6	7	8	9	10
A	B	A	A	B	A	B	B	A	

$\rightarrow 1 \rightarrow A$   
 $0 \rightarrow B$



## ① Complete Randomization

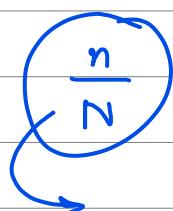
drugs  
A & B assign with equal prob.



using R → SRSWR  
① sample

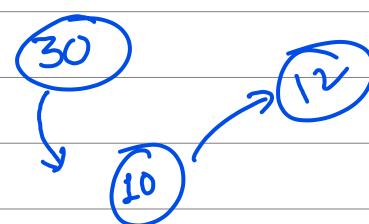
② Bernoulli: —  $0.5 \rightarrow L \rightarrow A$   
 $0 \rightarrow B$

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?

$$\frac{100}{10}$$

Sample fraction should be  $\frac{1}{10} \rightarrow \frac{1}{2}$

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 ✓

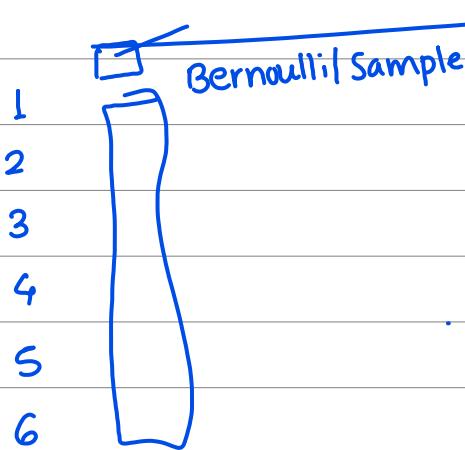
A 1 4 6 ✓  $n(A) = 3$

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	A
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

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

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

### \* Complete Randomization

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

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

$\therefore n_A + n_B \sim \text{Binomial}(20, 1)$

$P(n_A = 10) = P(n_B = 10) = \frac{20!}{10!10!} 0.5^{20}$

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

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

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

### \* 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

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  $\rightarrow$

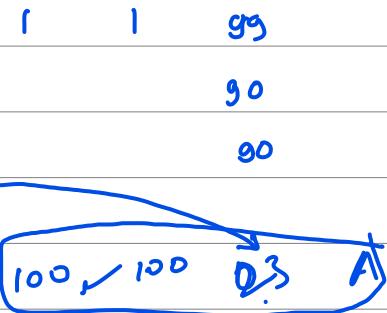
30 patients divided into 3 blocks

what if I want only 2 blocks

?	1	!	16	1	30 $\rightarrow$ 1
$n_A = 15$	2	$8-A$	$7-A$		$5 \rightarrow A$
$n_B = 15$		$T-B$	$8-B$		$5 \rightarrow B$
	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 50% perfect*

*Com. balance 5 M. 5 A. 5 B.*

*Treatment balance 5 M. 5 F. 0 O 5 ←*

*Comparable groups*

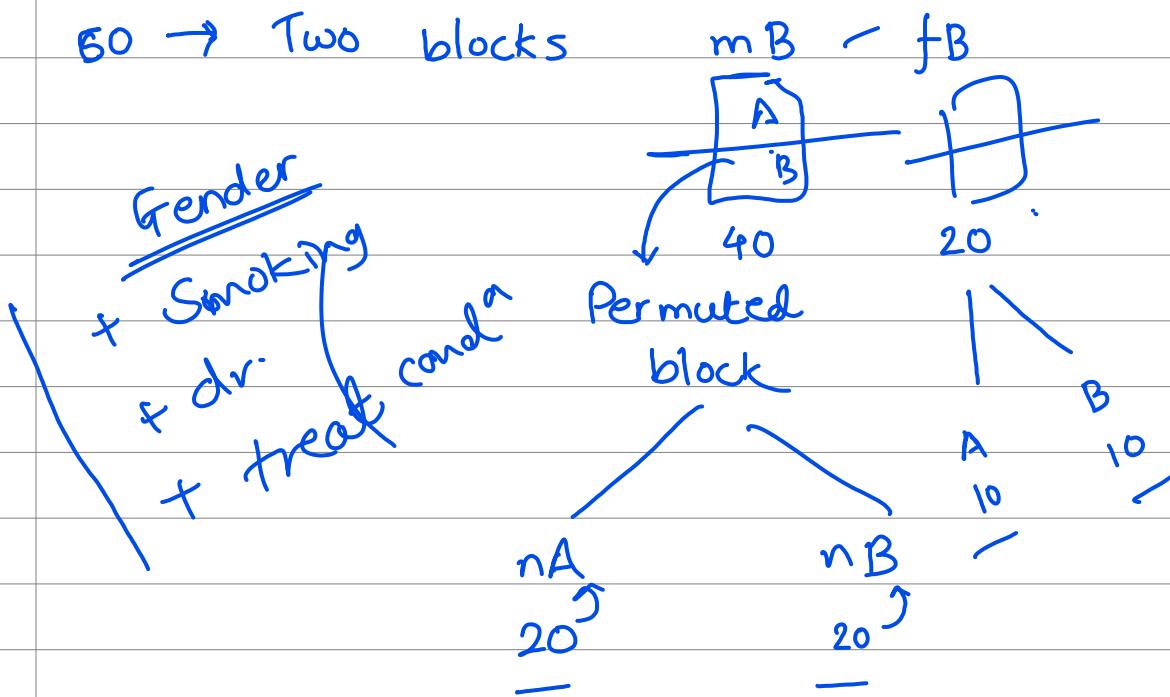
### Adaptive Randomizations

① Treatment Adaptive Randomization

② Covariate A R

(Stratified Randomization)

③ Response A R



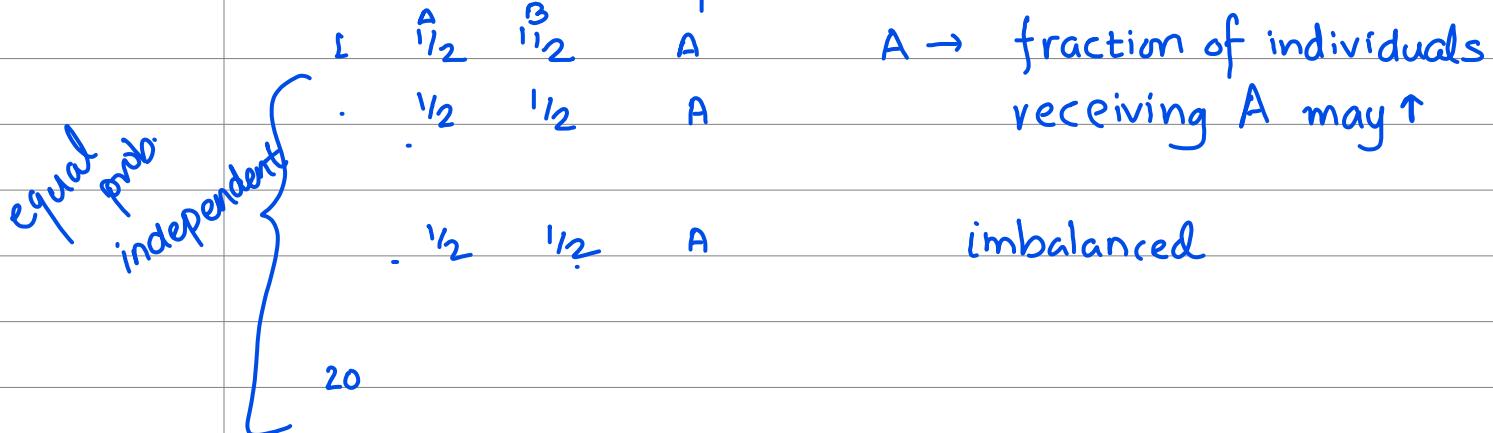
\* Covariate :- Strata  $\rightarrow$  Covariate - Seq's -

6 - SF      B-3  
6 - SM      A-3  
4 - NF      B-3

Covariate - Groups - ✓ Permutated

Complete - Randomiz. 4 - NM

\* Treatment Adaptive Randomization



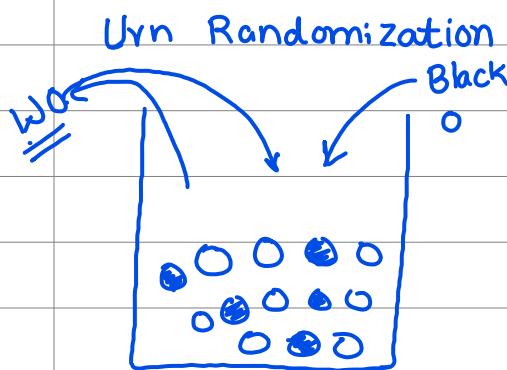
Efron (1971)

Biased coin randomization

	A	B	
✓ 1	$\frac{1}{2}$	$\frac{1}{2}$	$A'$
2	$\frac{1}{2} - \frac{1}{20}$	$\frac{1}{2} + \frac{1}{20}$	A
	$\frac{1}{2} - \frac{1}{20}$	$\frac{1}{2} + \frac{1}{20}$	B
	$\frac{1}{2} - \frac{1}{20}$	$\frac{1}{2} + \frac{1}{20}$	

$$\begin{array}{ccc}
 P & q & A \\
 P = P + \frac{1}{20} & q = q + \frac{1}{20} & A : \\
 P = \frac{1}{2} & q = \frac{9}{20} + \frac{1}{20} &
 \end{array}$$

20



White	Black	$P(W)$	Balance
$A = 15$	$A = 15$	$A/2A = \frac{1}{2}$	$1 : W \rightarrow A \checkmark$
$A$	$A + 1$	$A/(2A+1) < \frac{1}{2}$	$2 : B \rightarrow B \checkmark$
$A+1$	$A+1$	$\frac{1}{2}$	<u>30</u>

~~T A R code~~

no. of patients :- 30

~~A~~ $nW=15$     $nB=15$ 

Drug = c('T', 'R')

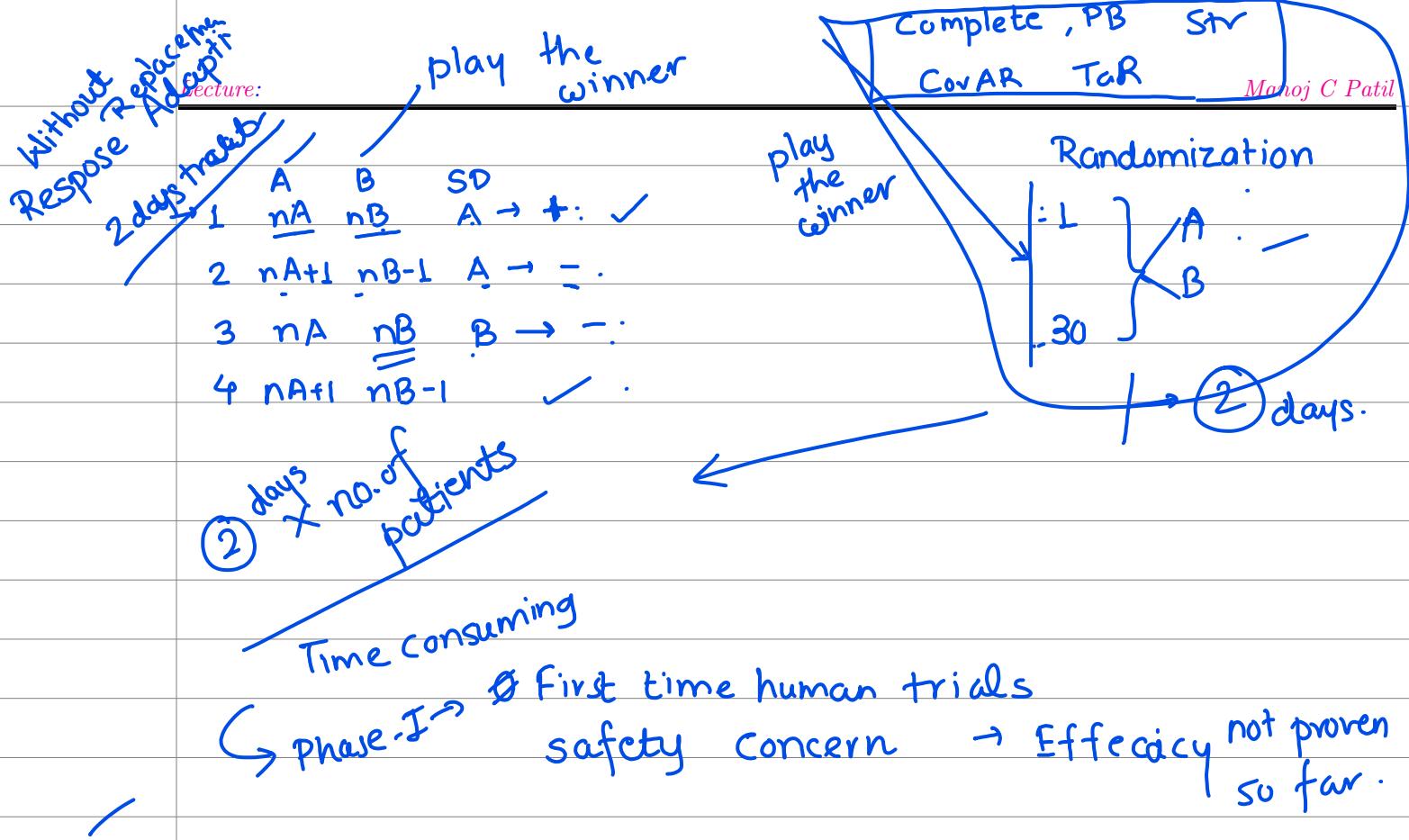
tre[1] =

✓ Sample(Drug, 1, replace=F, prob = (nW/(nW+nB), nB/(nW+nB)))

```

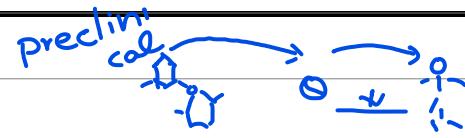
for (i=2:30){
  if(tre[i-1] == 'T') {nB=nB+1} else {nW=nW+1}
  tre[i] = Samp
}
  
```

\* Response Adaptive Randomization  
(Play the winner - )



$$\begin{array}{ll} n_A+1 & n_B-1 \\ n_A-1 & n_B+1 \end{array} \leftarrow \begin{array}{c|c} A+ & B- \\ A- & B+ \end{array}$$

Absent:- 2001, 2, 3, 4, 6, 9, 10, 12, 14, 16, 17, 23, 33, 34, 35, 43, 44, 45, 50, 51, 55 = 21 students  
Thank you.



## Phases- clinical trials

I  
mostly healthy  
20-80 subjects

II

100-1000  
IIA  
several hundreds subjects

IIIB

several thousands  
III  
several thousands

IV

other  
18-60 patients

Introduction - IND → first time human trials. Primary concern is safety, check effectiveness. ADME\* studies, Pharmacologic activity, (Most titration\* design), Therapeutic window, (Dose Ranges)

First time - well controlled CT. ① Effectiveness - ② Dose-Response Rel<sup>4 part</sup>

- Dose Range

extended phase II trials - Effectiveness

Physicians Label

↳ Additional info effectiveness & safety needed to identify benefit-risk relationship

⇒ Drug Approval & Process

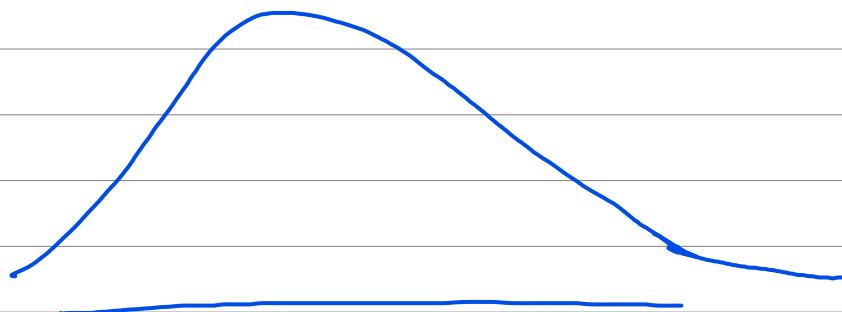
Trials → Phase IIIIB

Submission

After drug approval → Post market trials → Adverse Effect

Competitive — morbidity of mortality

\*ADME :- Absorption → Distribution → Metabolism → Excretion



\*Titration :- 1000 → Drug A → 50-60 died.

designs Instead → use 1 patient → observe

side  
1  
high

MED & MTD  
min effective tolerable

2 side  
lower  
Same

MED Therapeutic window MTD

\* Control ? ∵ Treatment

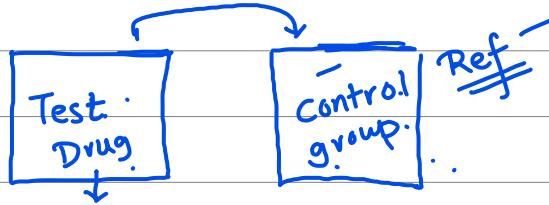
Ref: ① No treatment

② Placebo treatment

✓ ③ Active Drug

④ Dose-response concurrent

⑤ Historical concurrent



Drug is effective

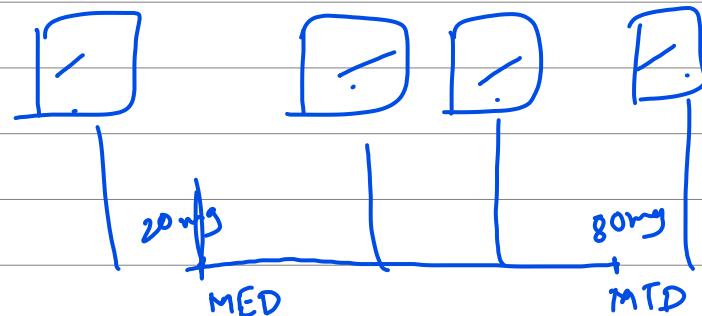
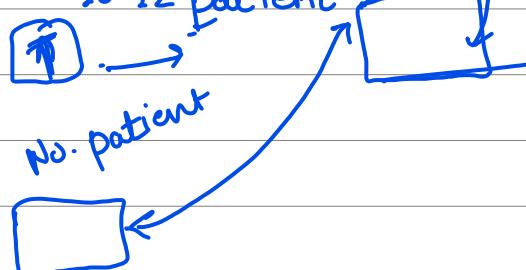
(Therapeutic window) concurrent control

↑  
Test

parac.

Rare disease :-

e.g. Brain tumor :-  
10-12 patient



\* Safety :-

Test

$$P(\text{Death/Test}) = 0.001 \text{ or } 0.00001$$

Phase-I ≈ 20-80 → may not observed

II      100-1000 → may

\* Investigational New Drug:

Commercial IND

① Leads to NDA

② Market purpose

③ Pharmaceutical companies  
sponsor

Non-commercial IND.

① May or may not be

② Research purpose

③ Sponsors.

\* NGOs

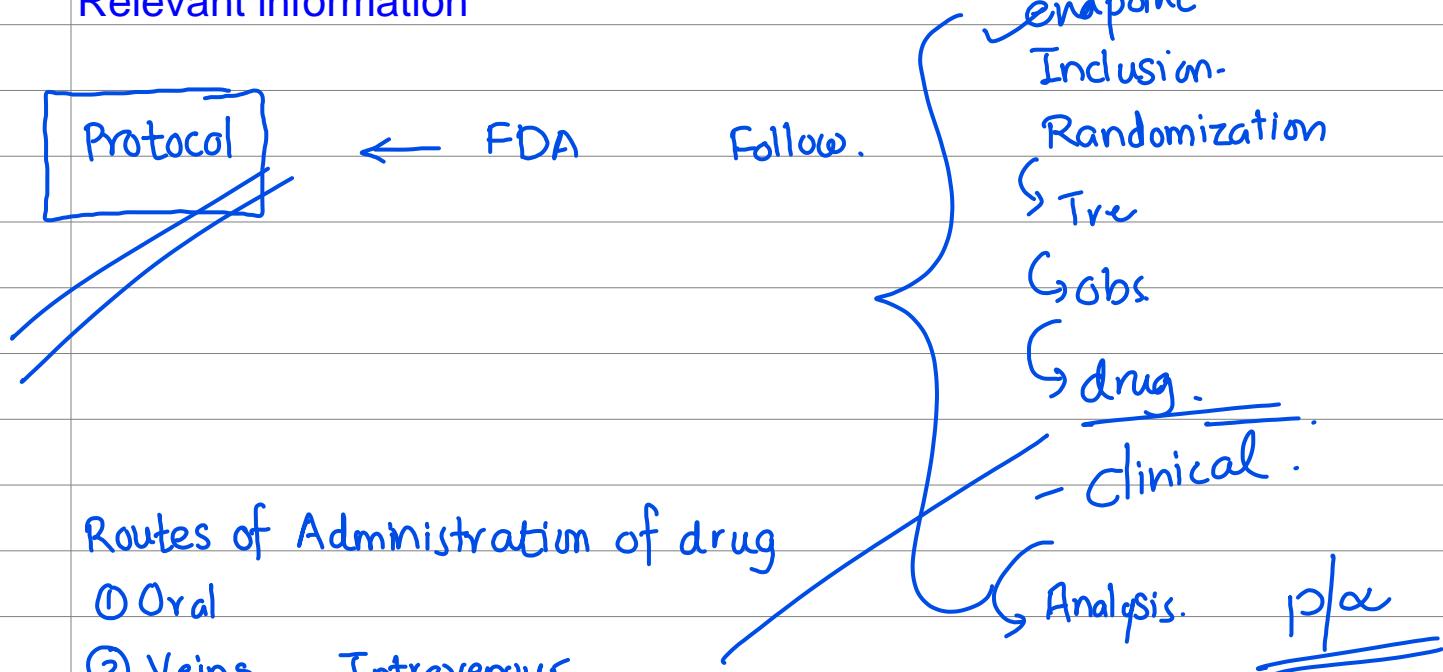
\* Govt Health dept

\* CROs (NARI, Cancer, I)

↳ Dr. Reddy, Reliance life  
(Glaxo).

## IND Documents to Accompany an IND Submission

- A cover sheet
- A table of contents
- The investigational plan
- The investigator's brochure
- ✓ Protocol
- Chemistry, manufacturing, and controls information
- Pharmacology and toxicology information
- Previous human experiences with the investigational drug
- Additional information
- Relevant information



### Routes of Administration of drug

- ① Oral
- ② Veins      Intravenous
- ③ Arteries
- ④ Nasal
- ⑤ Muscles. - Intramuscular
- ⑥ skin
- ⑦ \_\_\_\_\_
- ⑧ \_\_\_\_\_

- ① Oral
- ② Sublingual
- ③ Rectal
- ④ Topical
- ⑤ Parental      Intravenous-  
- Intramuscular  
- subcutaneous

Center 14 Test 01 Sub 001

1401001  
1502009  
= = =

Labelling

- potential bias

Protocol must contains

Concomitant Medicine ?

Test Drug + Milk ✓  
\* Drug B. ✓

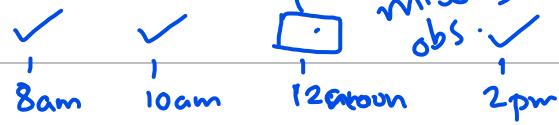
Ref

+ Milk ✓  
+ Drug B ✓

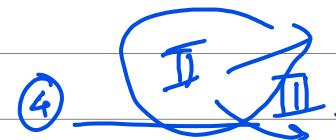
① Dropouts ? Treatment →

who fails to complete

② missing value



③ gmat → Premature Termination.  
④ 7 pre

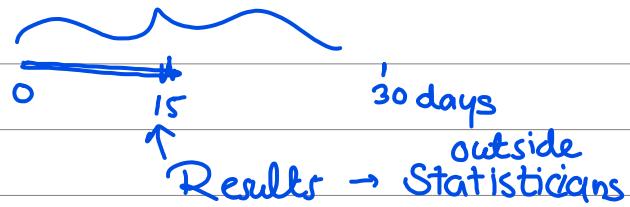


\* Multicenter Trials :- ?

① No. of pat subjects ↑

② Results generalizable

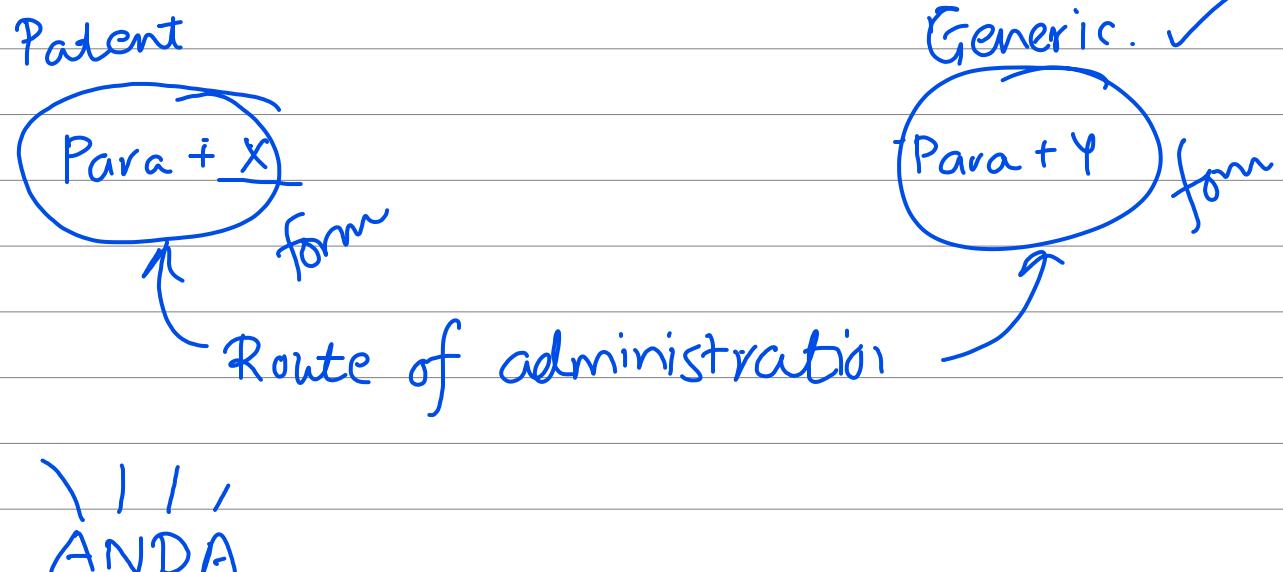
\* Interim Analysis



Absent.'r

2001, 4, 6, 12, 14, 16, 17, 18, 22, 25, 33, 34, 35, 43, 44, 45, 47, 50, 54, 55

Thank you.  
= 20 students



2001, 6, 7, 9, 10, 12, 16, 17, 21, 22, 25, 33, 35, 39, 43 to 47,  
50, 54, 55,

#### \* Designs for Clinical Trials

302

Design & Analysis of  
Expts.

o One-way - Two way

##### ① One way

- Single factor - significant or not on different levels / Treatment

Drug A:	0mg	250mg	500 mg
	Placebo	A	A

Drug Patient

A  $\rightarrow$  1  $\rightarrow$   $x_{11} x_{12} x_{13} x_{14}$   $\leftarrow$  Repeated Measurement  $\rightarrow$  2 2 2 2 4  $\rightarrow$  2 3

B  $\rightarrow$  2

$x_{21} x_{22} x_{24}$

C  $\rightarrow$  3

Note Effect  $\rightarrow$  then Anova

• Repeated Measurement  
• Replications?  
same treatment  
on diff. individuals

## Drugs Patients

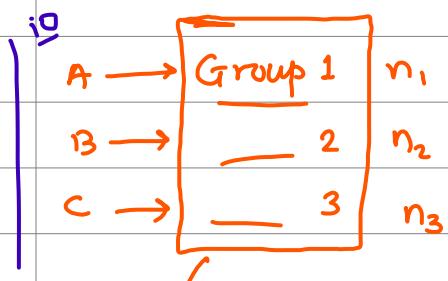
A.	<u>1, 4</u>	2
B.	2, 5, 8	3
C	3, 6, 7	3

Replication

## ① One-way

A B C

$\mu_A = \mu_B = \mu_C$

homogenous  
Group formation?Comparable  
Uniform

↳ Randomization? Unbiased

↳ Reduce-bias &amp; variability

Anova :- F dist

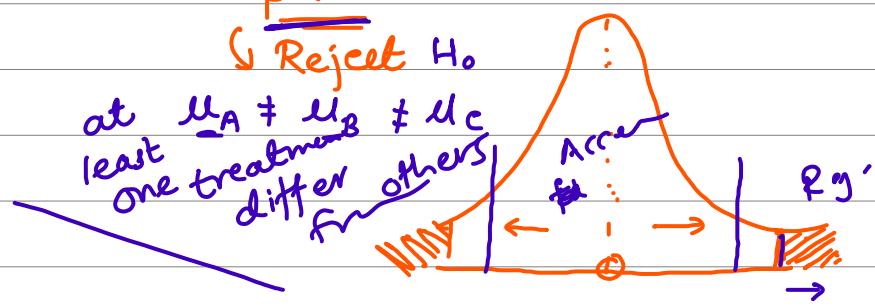
 $F_{crit-2}$  $F_c < F_{table}$ 

Fail to Reject

$\checkmark \mu_A = \mu_B = \mu_C$

p value

$p < \alpha$

↳ Reject  $H_0$ at  $\mu_A \neq \mu_B \neq \mu_C$   
least one treatment  
differ from others

## Post-hoc

## Pairwise Comparison

$\mu_A \quad \mu_B \quad \mu_C$

①  $\mu_A = \mu_B$

②  $\mu_A = \mu_C$

③  $\mu_B = \mu_C$

Bonferroni / Tukey  
t-test

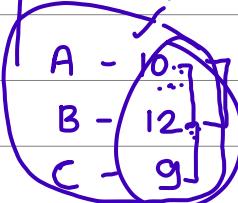
$$t = \frac{(\bar{x}_A - \bar{x}_B)}{\sqrt{MSE \left( \frac{1}{n_1} + \frac{1}{n_2} \right)}}$$

## Two-Sample t test

$$t = \frac{(\bar{x}_A - \bar{x}_B) - (\mu_A - \mu_B)}{\hat{\delta}_p \sqrt{\frac{1}{n_1} + \frac{1}{n_2}}}$$

Pooled

$$\hat{\delta}_p^2 = \frac{(n_1-1)\delta_1^2 + (n_2-1)\delta_2^2}{n_1+n_2-2}$$



## ② Two-way

Two factors - different levels

① Smoking habits

②

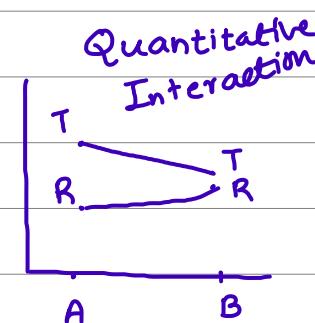
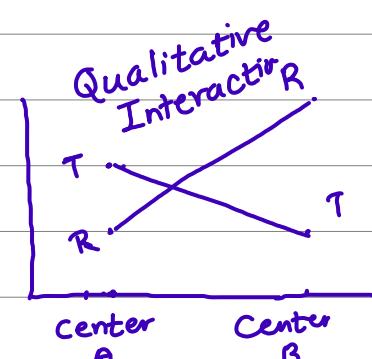
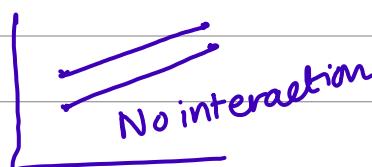
	Smoker	Non smoker
low	$n_1$	$n_2$
Moderate		
high		



$r$  fobs per cell

## ③ General two way

### Interaction Effect



## ④ Factorial Designs? -

$2^k$  factorial  
↑ No of factors  
levels.

	$B_1$	$B_2$	$B_3$
$A_1$	□	□	□
$A_2$	☒	☒	□
$A_3$			

## Two-way with inter

Treat Row	Row
Q1	1
Inte	2

Row	$r-1$
Colu	$c-1$
Inte	$(r-1)(c-1)$ ?
Error	
Total	

sign

→ MSF //  
→  $n_{-r,c}$   
error //  
error //

$$y_{ijk} = \mu + \alpha_i + \beta_j + (\alpha\beta)_{ij} + \epsilon_{ijk}$$

## Interaction

effect identify

## Confounding ?

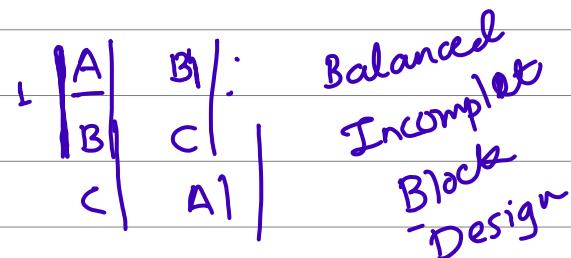
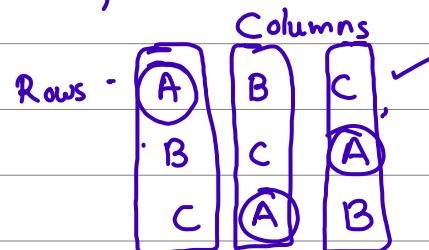
- due to some identified/unidentified factor effect

CRD RBD  
1 2 3 Factorial

LSD

Latin Square Design

3 factors



## Designs CT

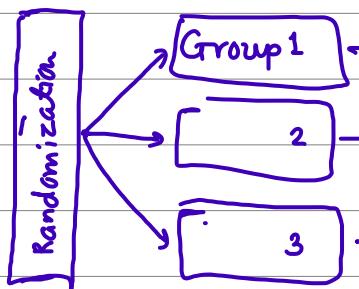
Obs: ① Test treat > better  
Refere

- ① Objectives → Treatment
- ② Other Factor → clinical endpoint →
- ③ Design → Analysis

Control :-

Active Concurrent Controls

## \* Parallel Group Design      3 treatment A, B, C



## Categorical

# Run-in Period

## Training

## Analysis ? ① Anova

## Assumption Normal

## ② Cat Anova

### ③ $\chi^2$

4

## 2 treatment ① t-test

$$\textcircled{2} \quad x^2$$

### ③ Non parametric

## Matched Pair

A                      B

160-165 1     $\longleftrightarrow$     3 160-165

150-155 2.     $\longleftrightarrow$     5 150-155

185-70 4     $\longleftrightarrow$     6.

- {1,3}
- {2,5}
- {4,6}

Abs :=

4, 6, 9, 10, 13-14, 16, 22, 30, 33-35, 39, 43-47, 50, 51, 53-55

= Total present  
37





























































































































































































































































































































































