

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

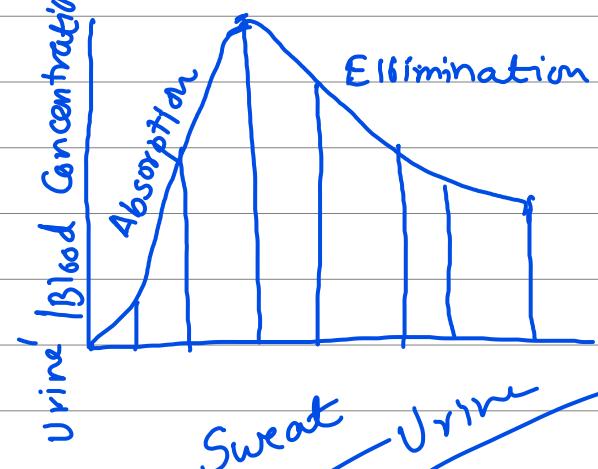
## Pharmacology

### 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  $\rightarrow$   
 $\text{due to } x$   $\rightarrow$   $0.0001$

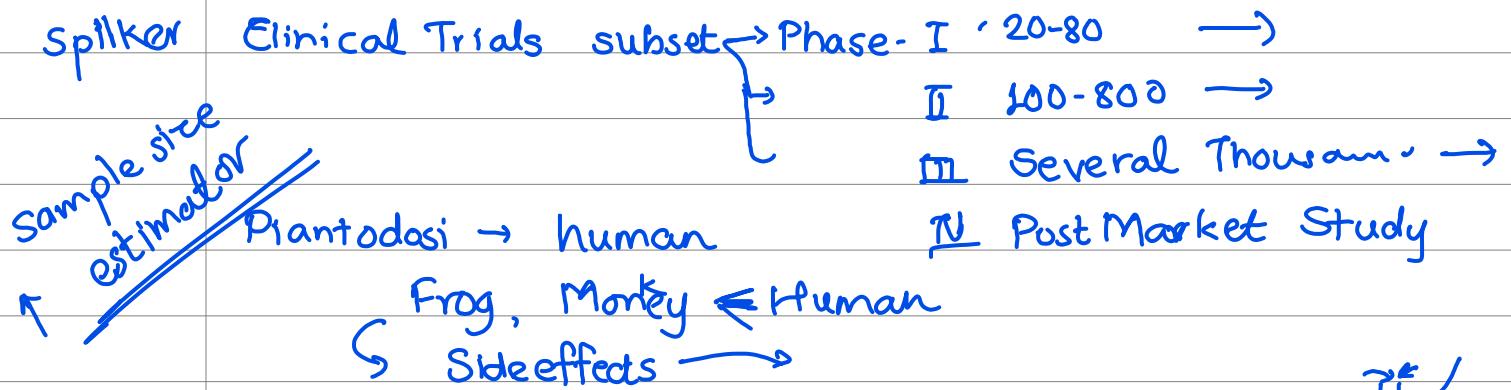
Phase-I  
Life threatening  
side effects

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

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

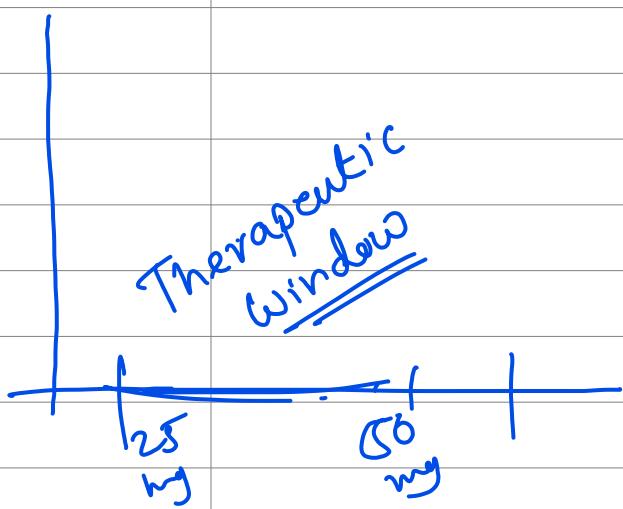
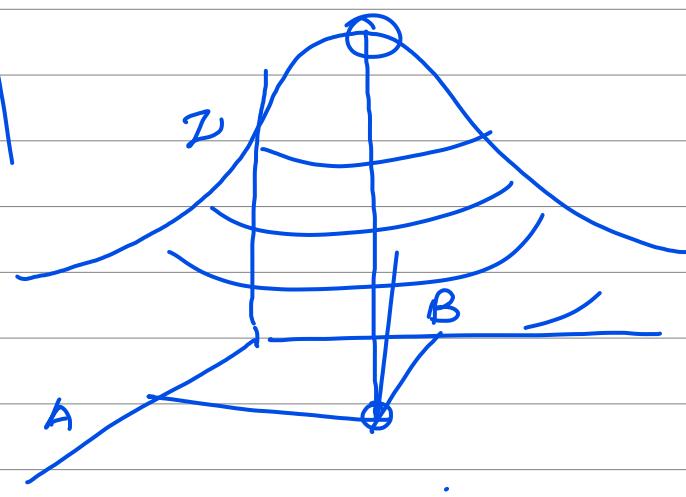
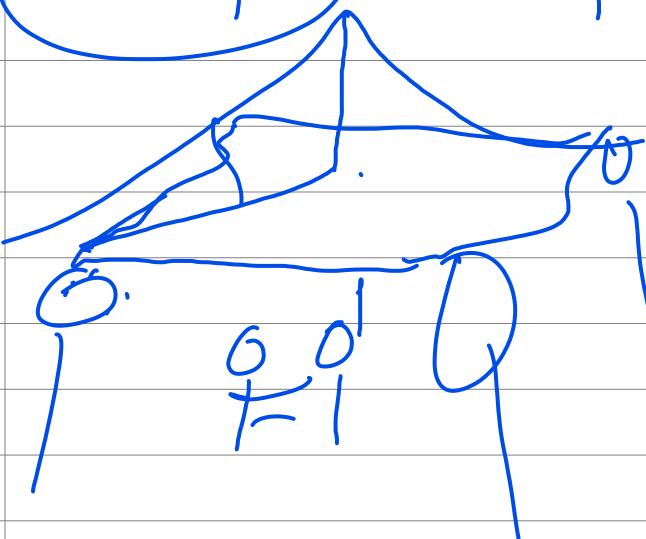
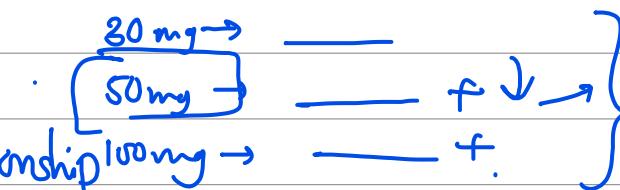
$\rightarrow$  Thousands  $\rightarrow$  Physicians labelling

$\rightarrow$  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

$C_p$  ?

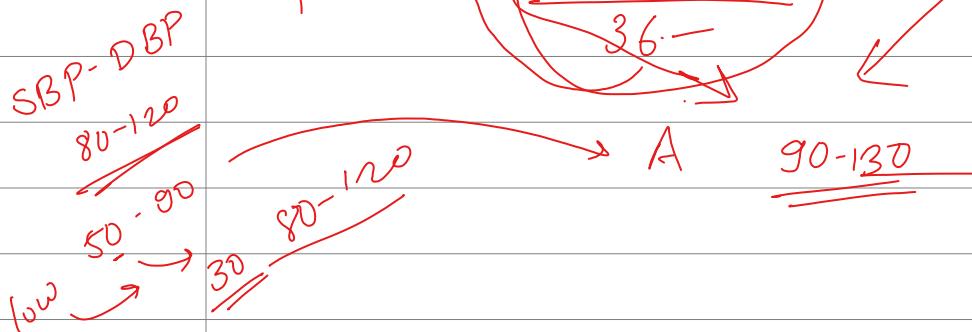
UST - LSL

36 -

Clinical diff

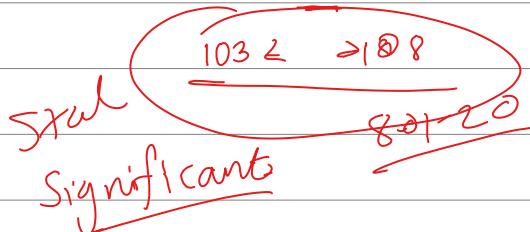
LSL ? USL ?

Clinician / Doctors



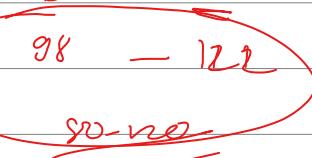
$$A \rightarrow \mu_A = 105$$

$$\delta_A = 1$$

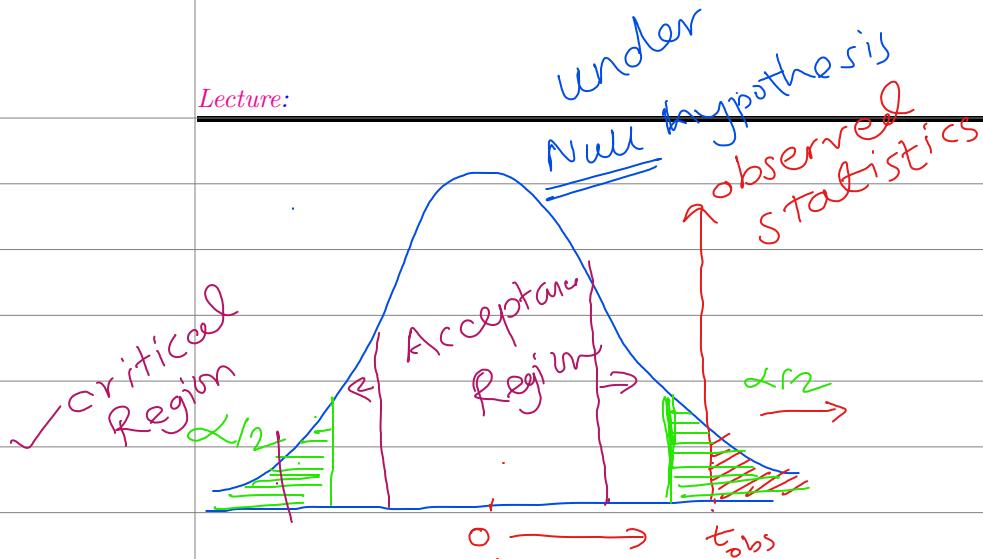


$$\beta = \mu_B = 110$$

$$\delta_B = 2$$



Clinician



$\alpha > p \rightarrow$  Reject  $H_0$   
 $p < \alpha \rightarrow$  Reject  $H_0$   
 $p > \alpha \rightarrow$  fail to Reject  $H_0$

Two way  $H_0 \Rightarrow \underline{\bar{u} = \bar{u}_0} \Rightarrow 2(1 - \text{CDF})$

One way  $H_0 \vdash \begin{cases} \underline{\bar{u} \geq \bar{u}_0} \Rightarrow 1 - \text{CDF} \\ \underline{\bar{u} < \bar{u}_0} \Rightarrow \text{CDF} \end{cases}$

*Confusion*  
*Rohan Sir*

## Patent

Trademark filed (Branded)

Active ingredient (x)

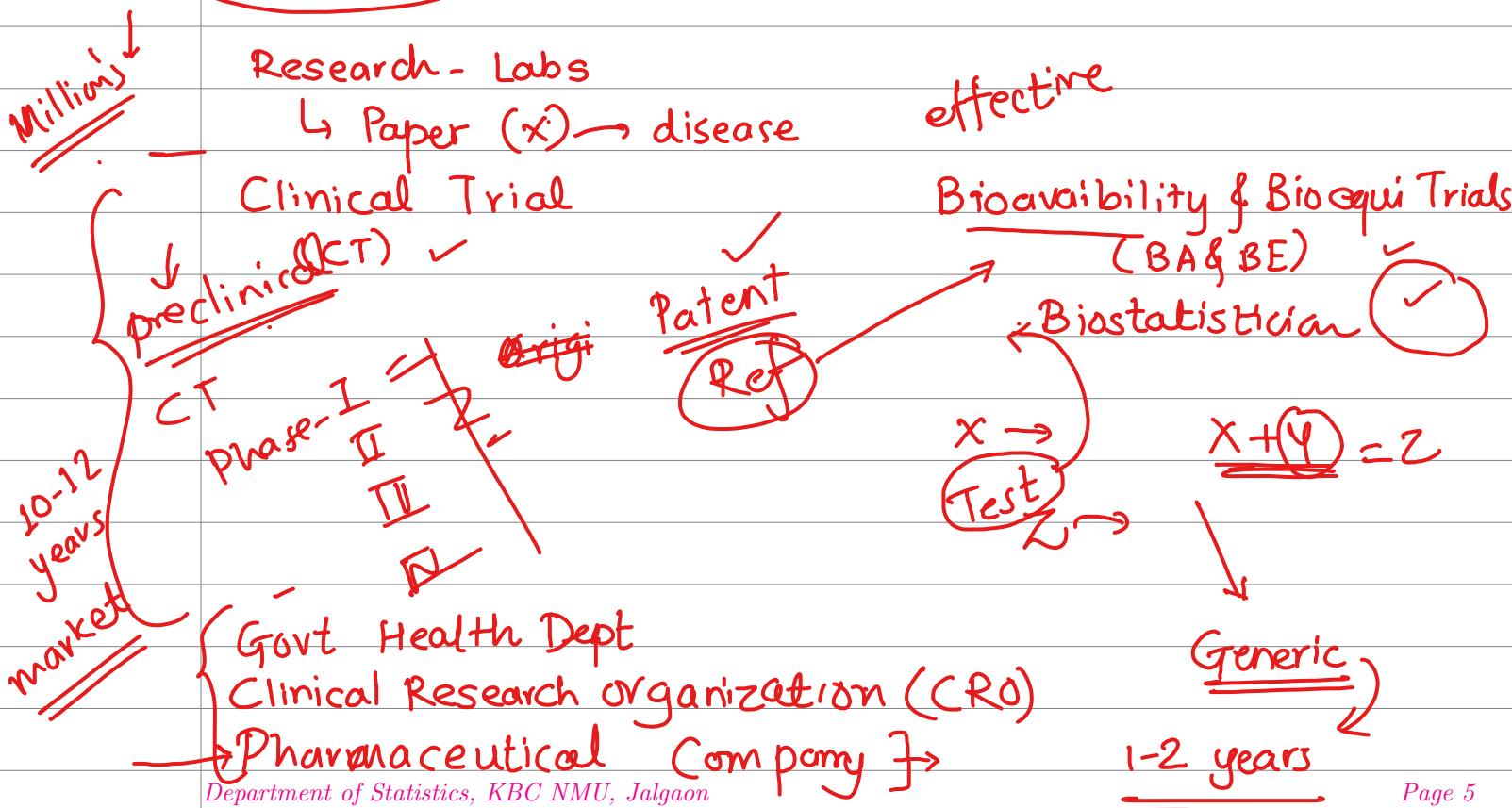
Inactive ingre

## 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	—	—	—

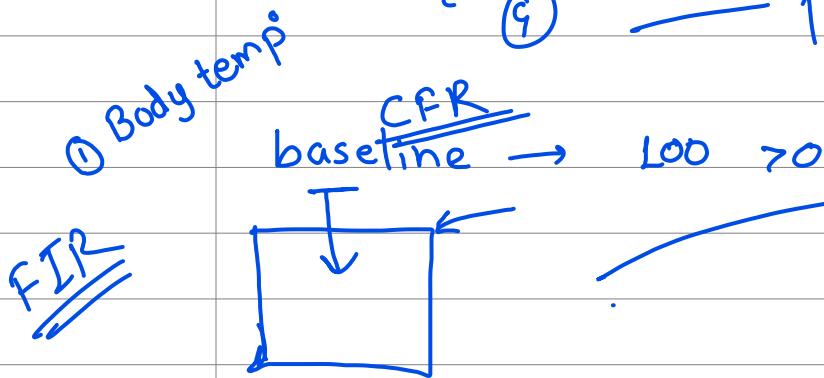
Objectives

①	—	—	✓
②	—	—	✓
③	—	—	✓
④	—	—	—

Objectives

①	—	—	✓
②	—	—	✓
③	—	—	✓
④	—	—	—

Fever ↓  
Cold ↓  
Sweat ↓



effective or not  
clinical endpoint  
≤ 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 \_\_\_\_\_

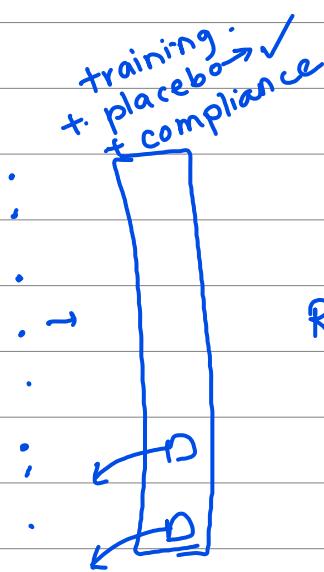
⑤ \_\_\_\_\_

Some inclusion & all exclusion criteria  
follow  
not followed

Run-in Period

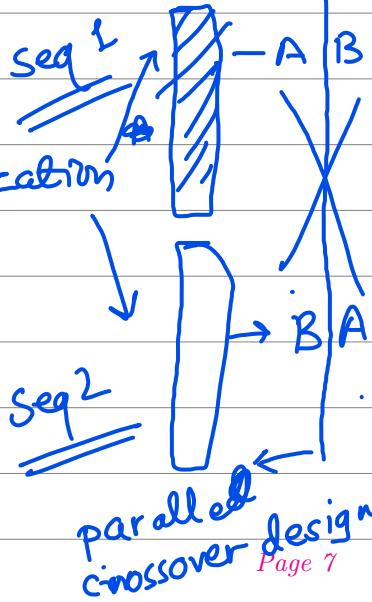
inclusion &  
exclusion  
criteria

Titration  
design



+ training  
+ placebo  
+ compliance

Randomization



parallel  
crossover design

?

Titration design - ①

②

③

④

⑤

⑥

Upward

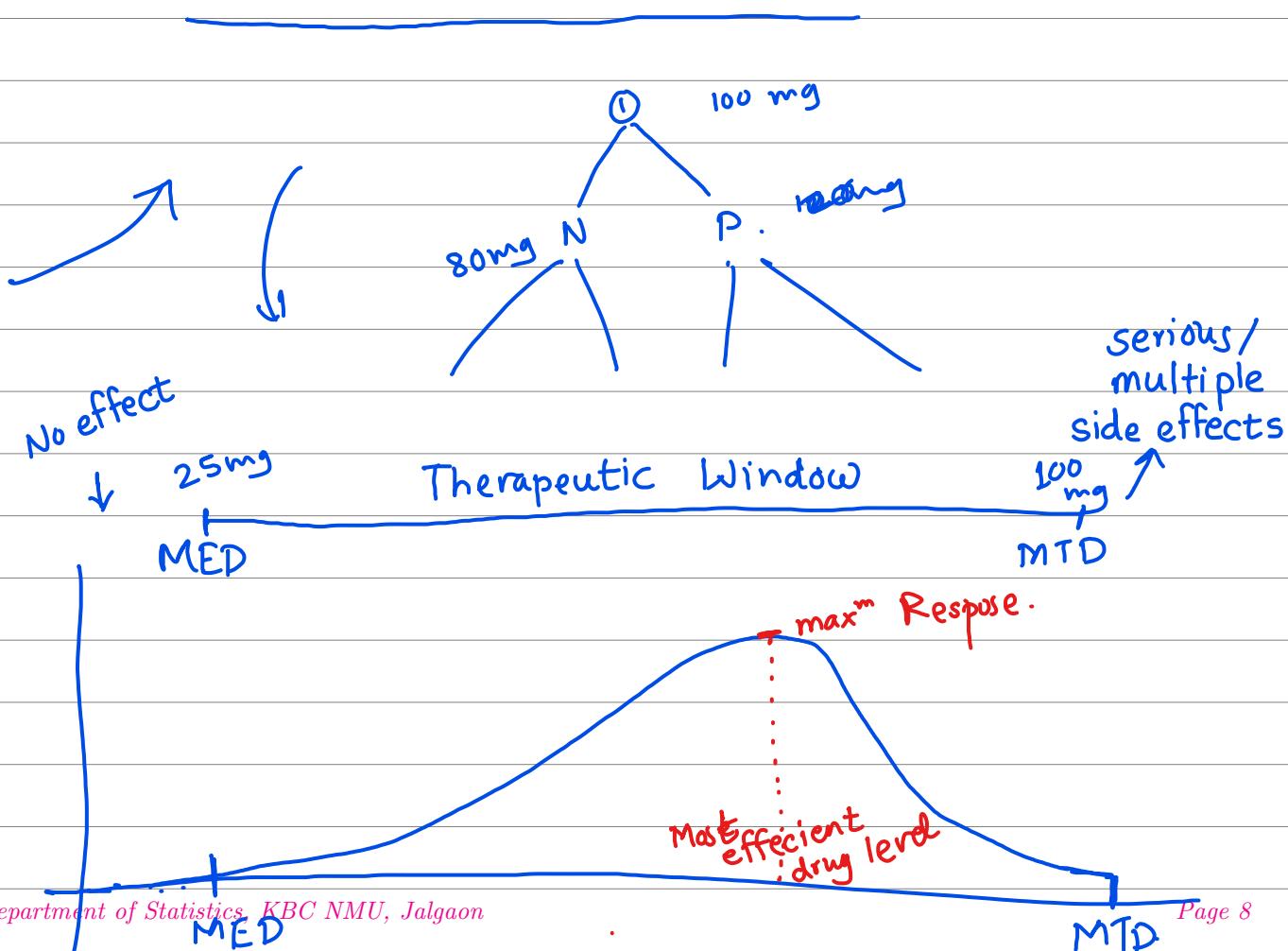
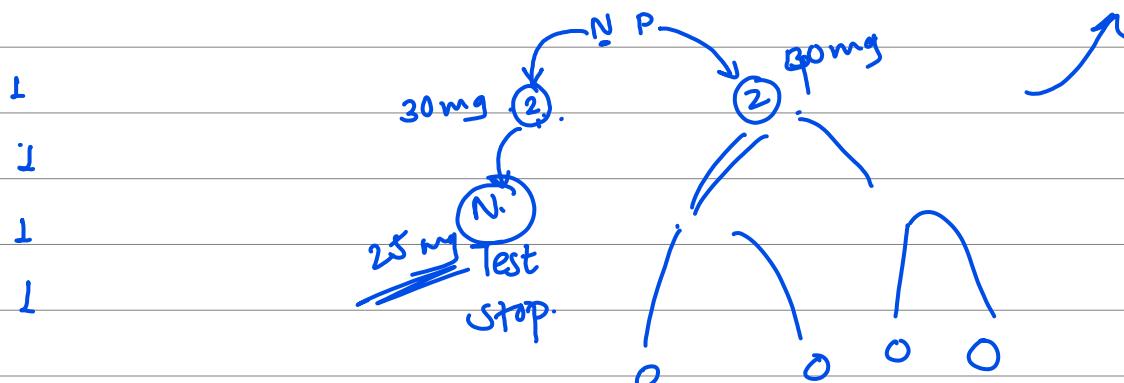
Upward-downward

downward

Human

Safety

① . 30mg -



## ① Methods of blinding

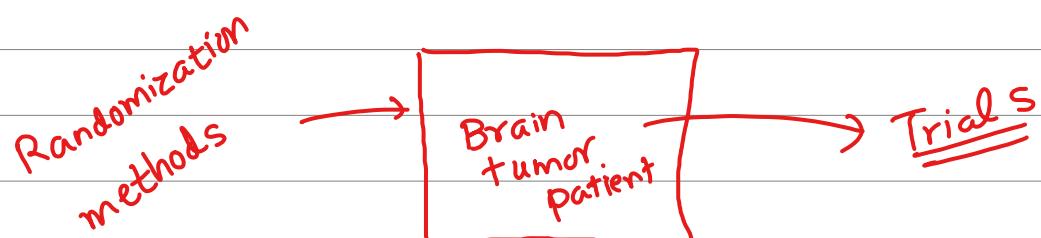
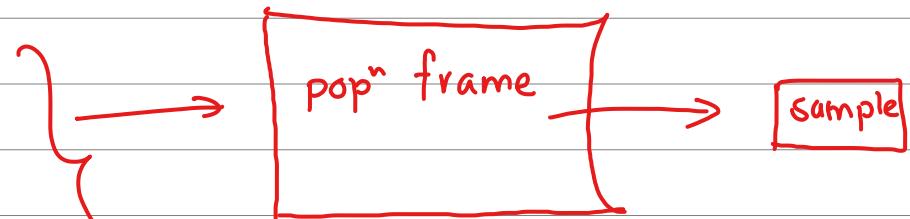
- open label** ① No - Everyone knows
- ② Single - Patient / Dr. any one is blinded
- ③ Double - & no one knows the allocations
- ④ Triple - Patient / Dr / Other staff all are blinded  
↳ Data collectors - Nurse

Data Analysts - Statisticians

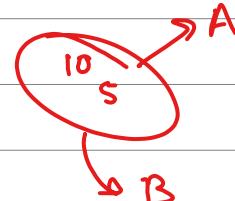
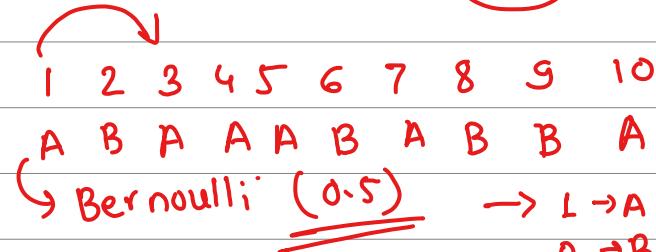
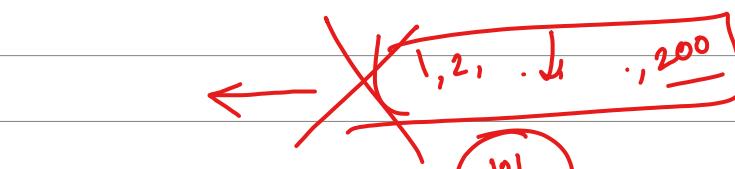


### \* Randomization ✓

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

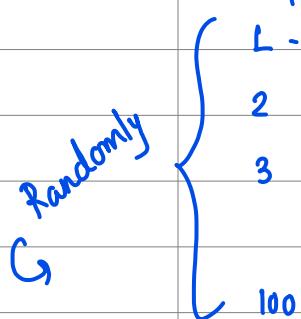


Randomization  
Assignment of patients to treatment groups



## ① Complete Randomization

drugs  
A & B assign with equal prob.

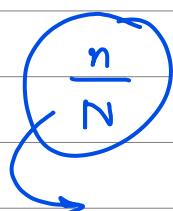


using R → SRSWR

① sample

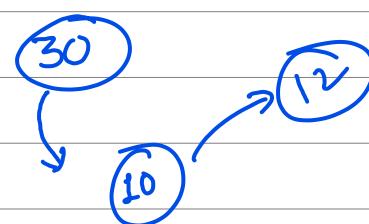
② Bernoulli: —  $0.5 \rightarrow L \rightarrow A$   
 $0 \rightarrow B$

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 ✓

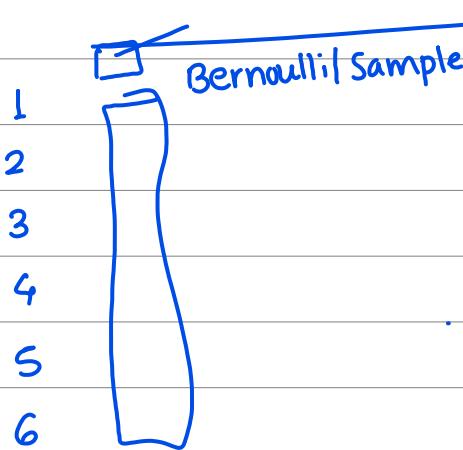
A 1 4 6 ✓       $n(A) = 3$

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	A
3	A	B
4	B	A
5	B	A
6	B	B

③

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

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

$\frac{1}{3} \rightarrow A$   
 $\frac{2}{3} \rightarrow B$

### \* 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	9	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

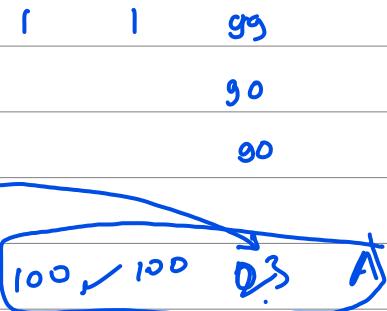
what if I want only 2 blocks

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

$$\begin{cases} 5 \rightarrow A \\ 5 \rightarrow B \end{cases}$$

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*

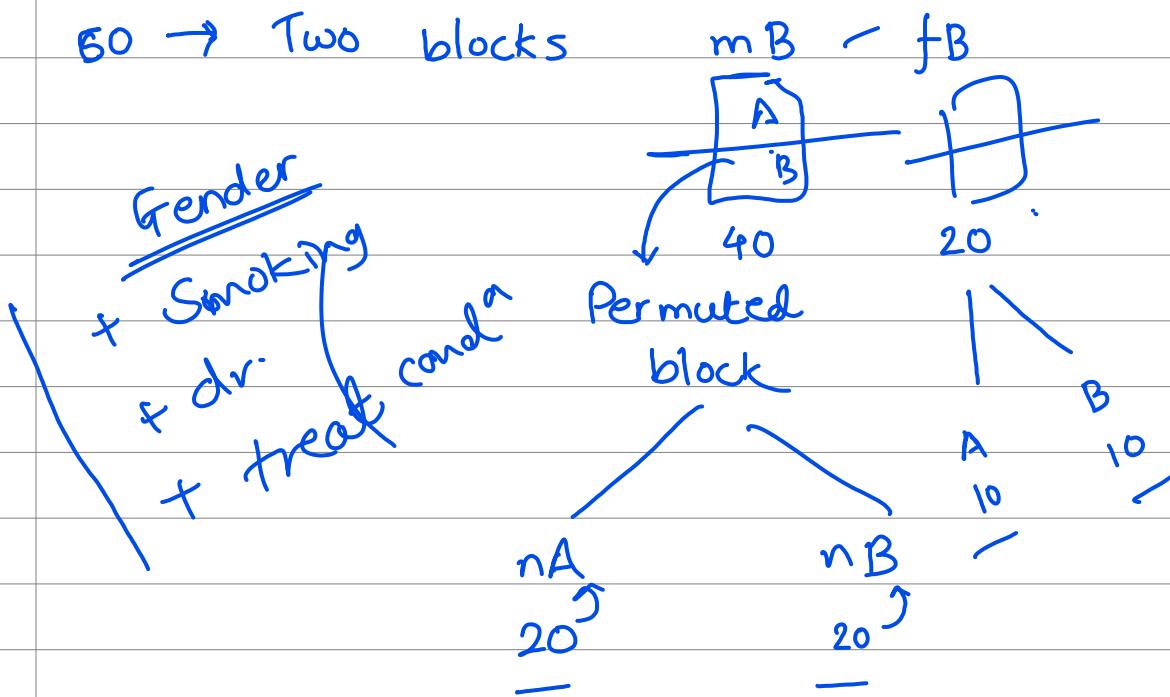
### Adaptive Randomizations

① Treatment Adaptive Randomization

② Covariate A R

(Stratified Randomization)

③ Response A R



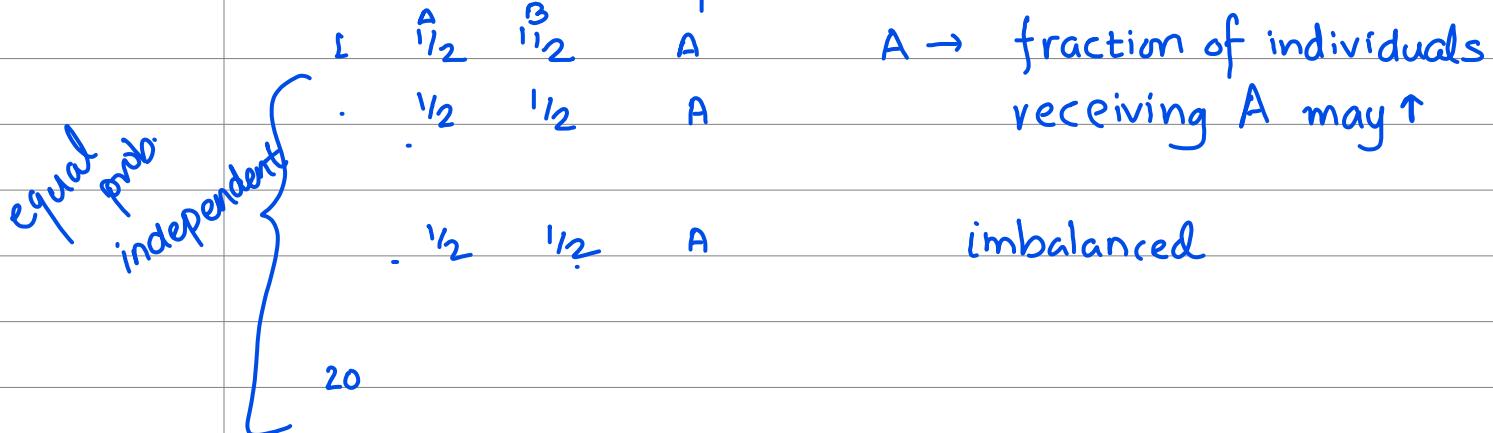
\* Covariate :- Strata  $\rightarrow$  Covariate - Seq's -

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

Covariate - Groups - ✓ Permutated

Complete - Randomiz. 4 - NM

\* Treatment Adaptive Randomization



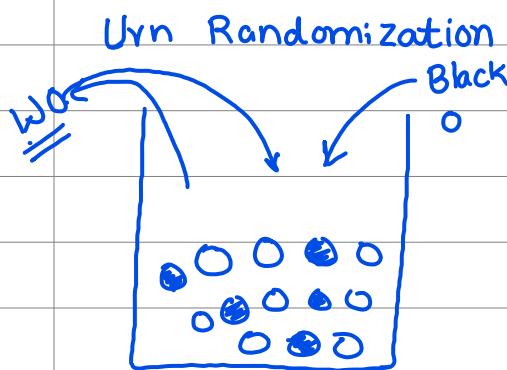
Efron (1971)

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

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

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')

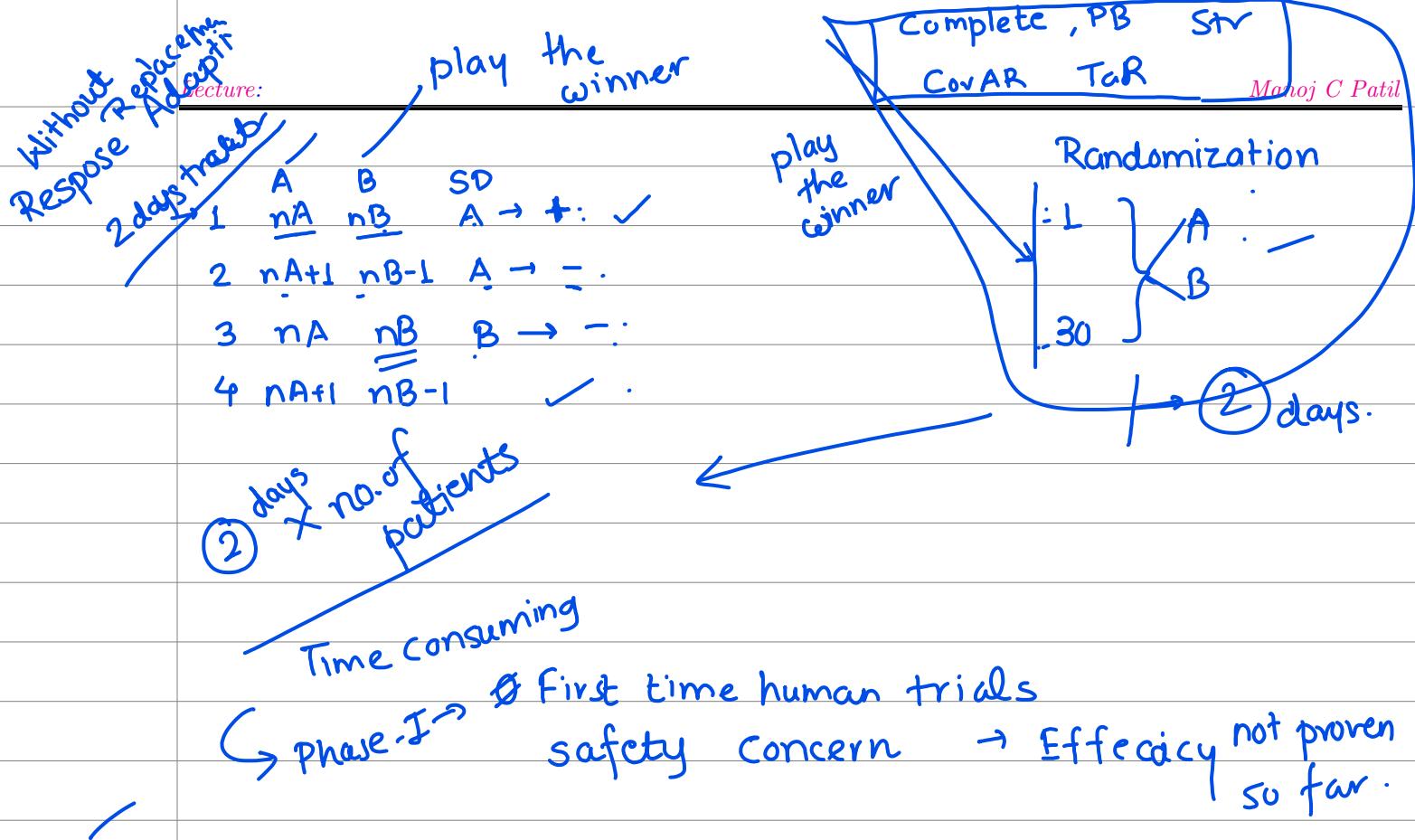
tre[1] =

✓ 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
}
  
```

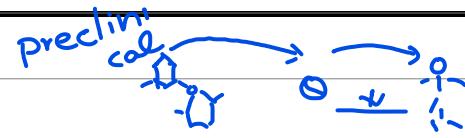
\* Response Adaptive Randomization  
(Play the winner - )



$$\begin{array}{ll}
 nA+1 & nB-1 \quad \leftarrow A+ / B- \\
 nA-1 & nB+1 \quad A- / B+
 \end{array}$$

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  
several hundreds subjects

II A

II B

several thousands  
several thousands

III

IV

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 III B

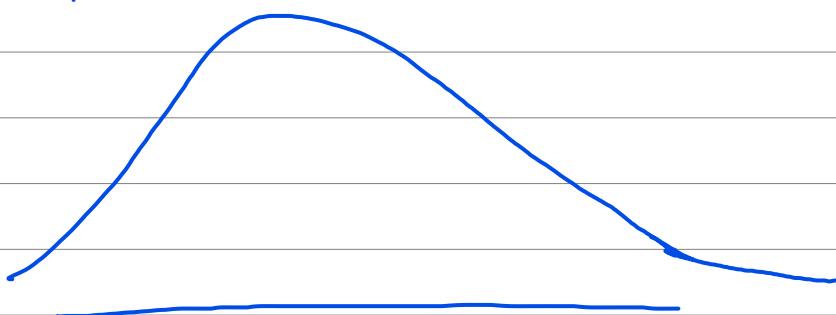
Submission

After drug approval → Post market trials → Adverse Effect

Competitive — morbidity of mortality

~~other~~ 18-60 patients

\*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  
1  
same

MED Therapeutic window MTD

\* Control ? ∵ Treatment

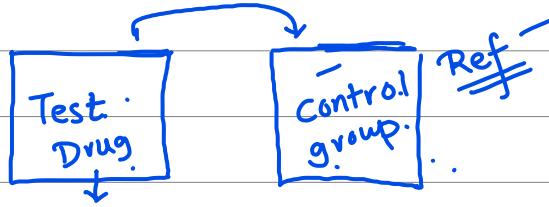
Ref: ① No treatment

② Placebo treatment

③ Active Drug

④ Dose-response concurrent

⑤ Historical concurrent



Drug is effective

(Therapeutic window) concurrent control

↑  
Test

parac.

Rare disease :-

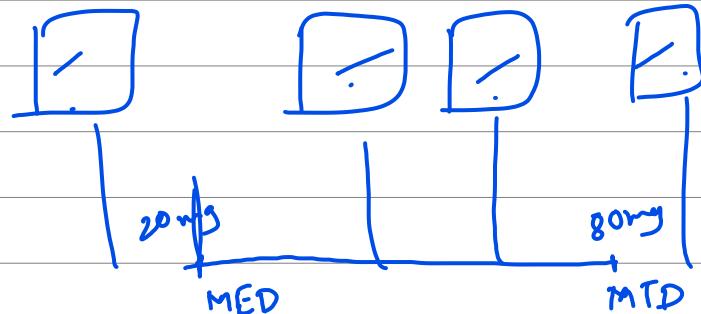
e.g. Brain tumor :-  
10-12 patient



No. patient



1985  
assume =



\* Safety :-

Test

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

Phase-I  $\approx 20-80 \rightarrow$  may not observed

II  $100-1000 \rightarrow$  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

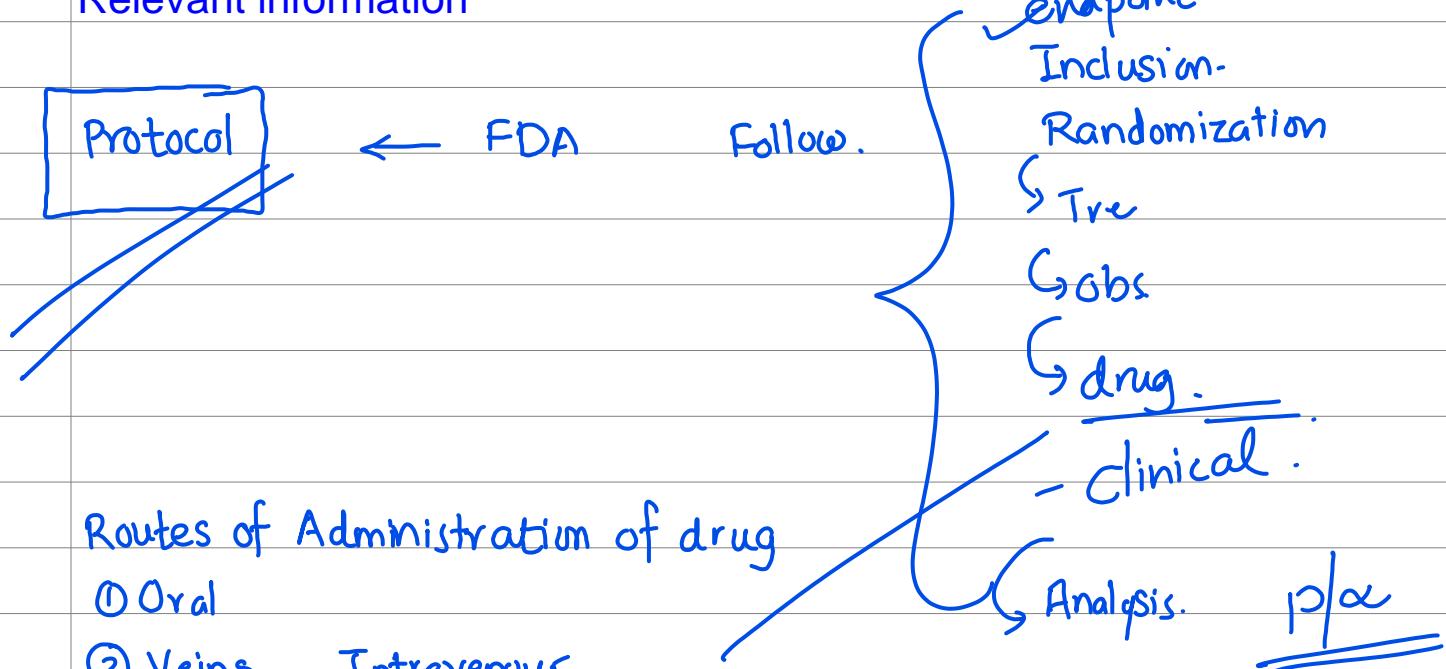
\* Govt Health dept

\* 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



- 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 Test Sub  
14 01 001

1401001  
15 02 009  
                    

Labelling

- potential bias

Protocol must contains  
✓ Concomitant Medicine ?  
Test Drug + Milk ✓  
\* Drug B. ✓

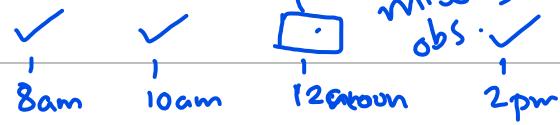
Ref

+ Milk ✓  
+ Drug B ✓

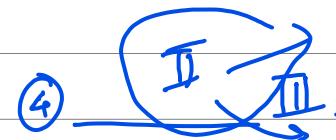
① Dropouts ? Treatment →

who fails to complete

② missing value



③ gmat → Premature Termination.  
④ 7 pre

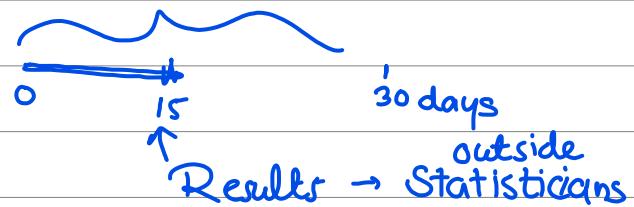


\* Multicenter Trials :- ?

① No. of pat subjects ↑

② Results generalizable

\* Interim Analysis

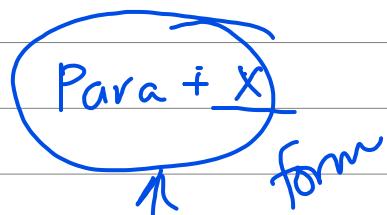


Absent.'r

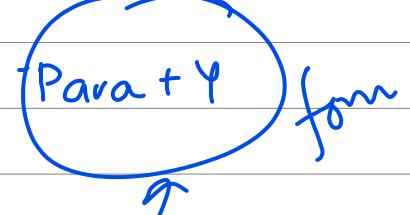
2001, 4, 6, 12, 14, 16, 17, 18, 22, 25, 33, 34, 35, 43, 44, 45, 47, 50, 54, 55

Thank you.  
= 20 students

Patent



Generic. ✓



ANDA  
111

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





































































































































































































































































































































































