

Evaluation :- Experiment → positive effective → max^m
 (side-effect → min^m)
 of treatment

US-FDA - Food, Drug, Administration

Weight loose $80 \rightarrow 60$ ^{min} side effect →
 Cost-optimization - Cost benefit
 cost-eco
 Radiations - Genes \Rightarrow pharmacogenomics } ✓

Evaluation

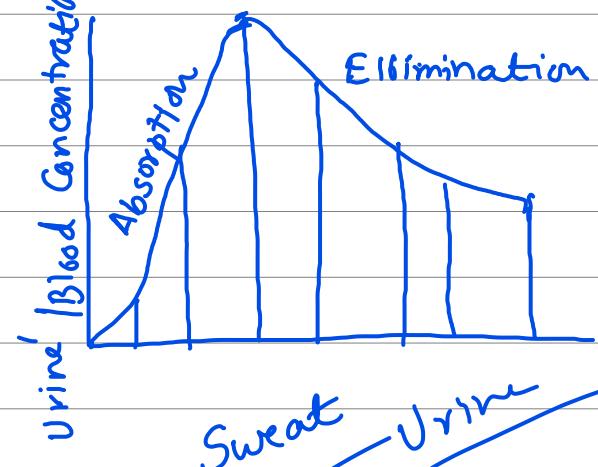
Pharmacology

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

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

Phase-I

\rightarrow 20/80 \rightarrow side effects min

II

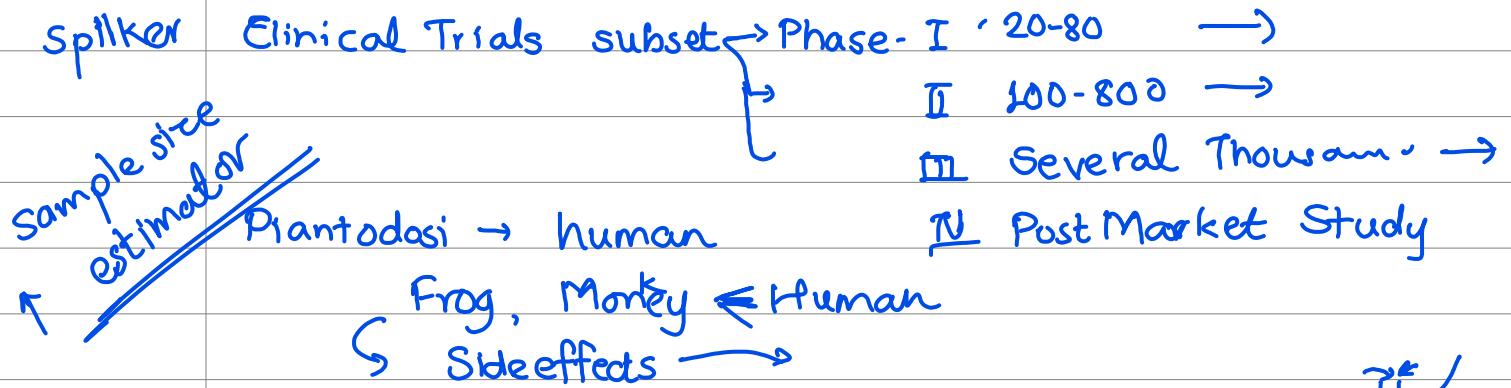
\rightarrow 800 - 1000 \rightarrow effectiveness side effect

III

\rightarrow Thousands \rightarrow Physicians labelling

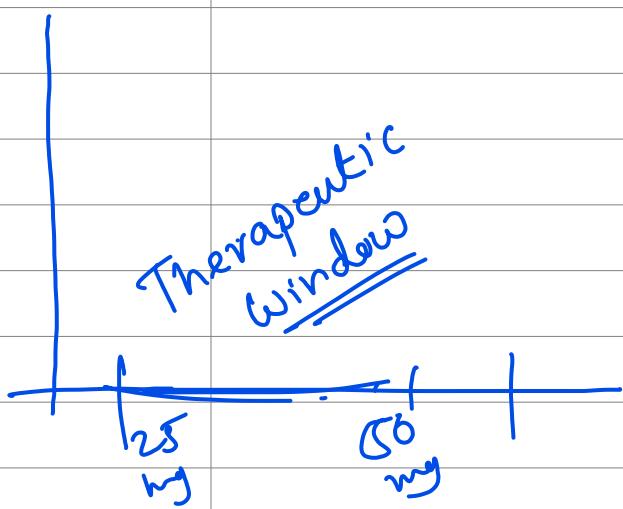
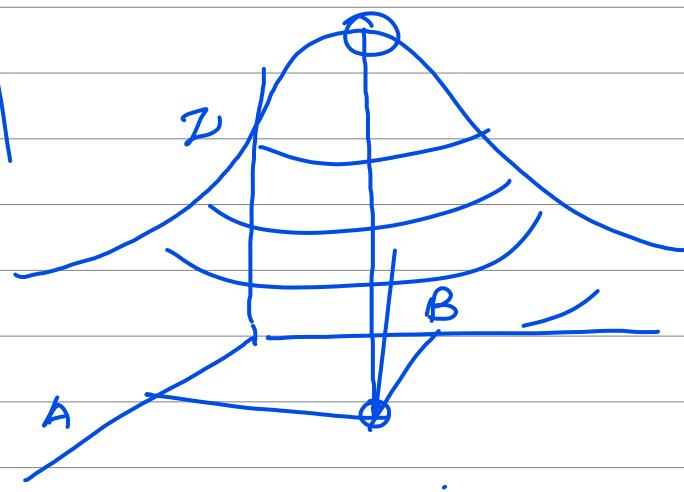
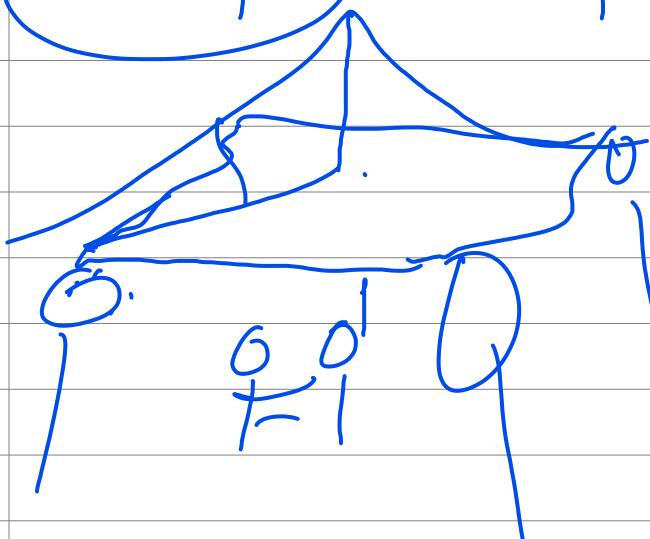
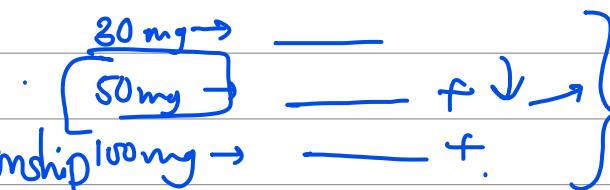
IV

\rightarrow Post Market Analysis



Titration Design

Dose-Response Relationship



10mg
50mg
80mg

MED - Min^m Effective Dose
 MTD → Max^m Tolerable Dose

0.00001 Life threatening side effect Physicians label

μ_p
Placebo ~~(X)~~

- ✓ ②
- ✓ ③
- ✓ ④

μ_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

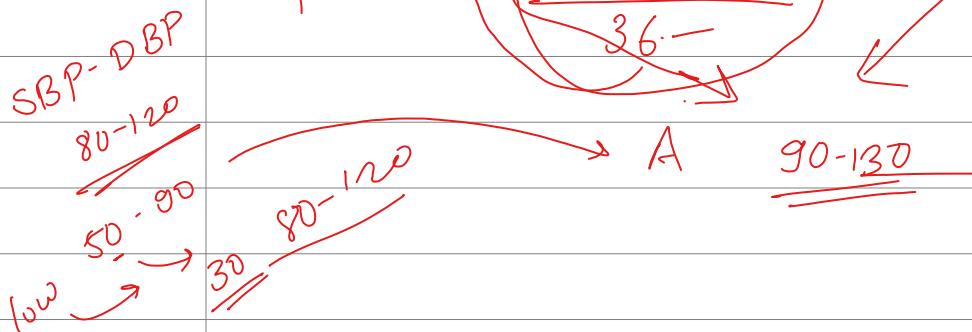
36 -

Clinical diff

LSL ?

USL ?

Clinician / Doctors



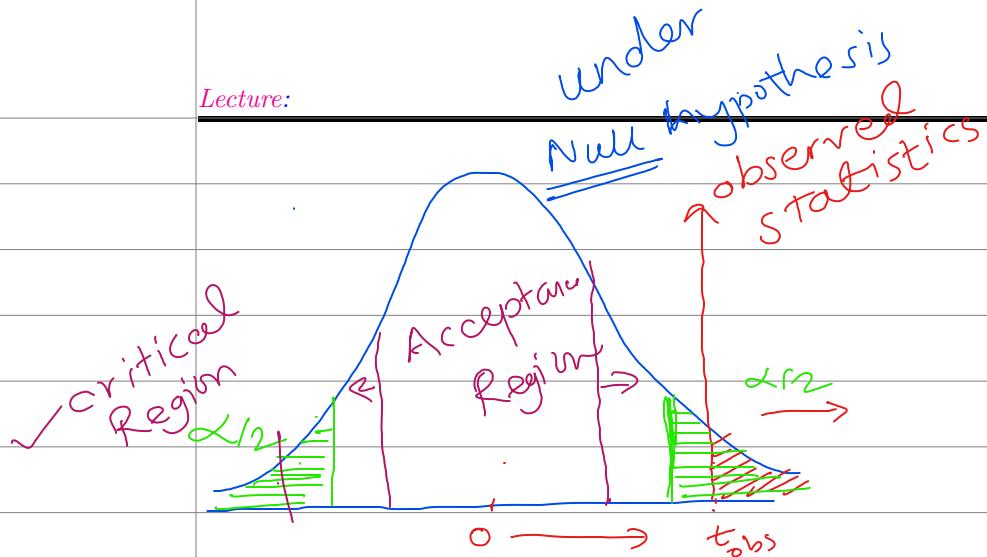
$$\beta = \mu_B = 110$$

$$\delta_B = 2$$

$$98 - 122$$

some

Clinician



$$\alpha > p$$

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

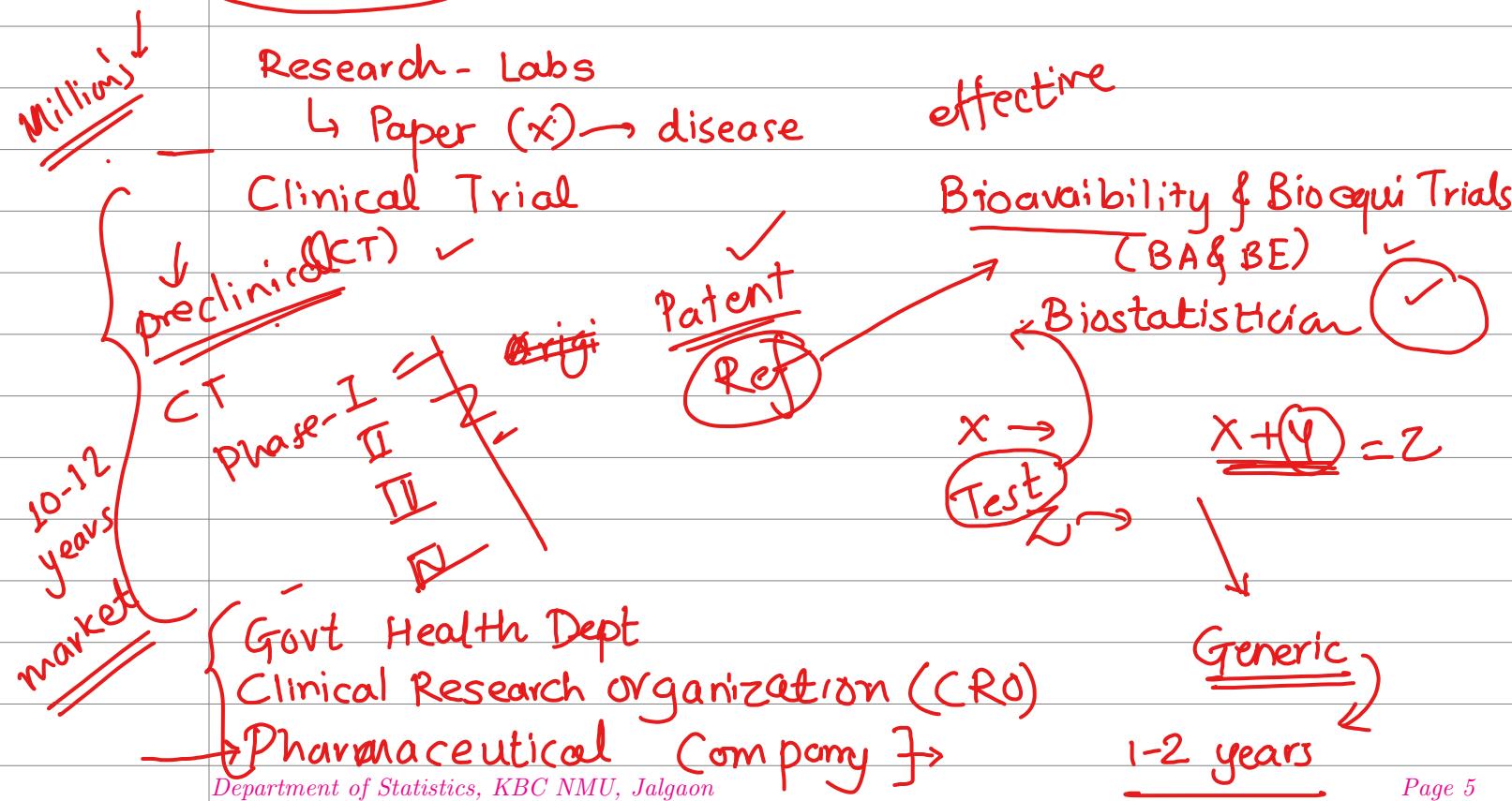
$p > \alpha \Rightarrow \text{fail to}$

$\text{Reject } H_0$

~~Confusion~~
~~Rohan Sir~~

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

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



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

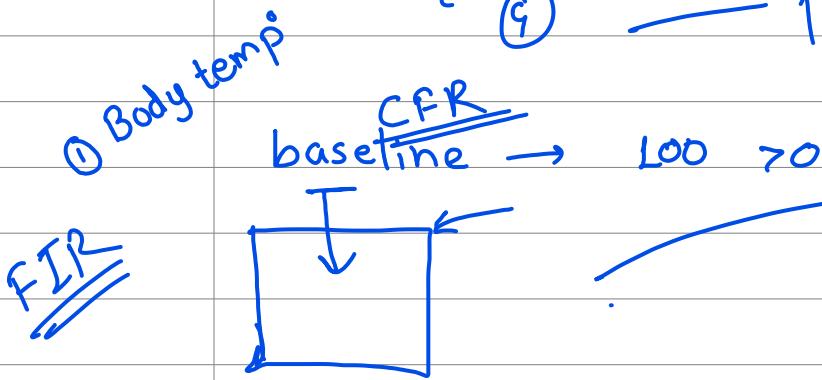
- ① Treatment to reduce weight
- ② Immunity
- ③ Muscles

Objectives

①	—	—	✓
②	—	—	✓
③	—	—	✓
④	—	—	—

Object

- ① Fever ↓
- ② Cold ↓
- ③ — ↓



effective or not
clinical endpoint
 ≤ 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 & ≥ 60 old age Exclude

② Feeding mother / pregnant

③ History disease

Medications

④ _____

⑤ _____

Inclusion
Some

Disease.

Healthy volunteer

③ > 18

④ _____

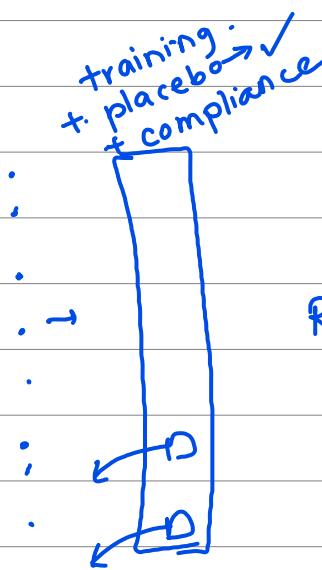
⑤ _____

Some inclusion & all exclusion criteria
follow
not followed

Run-in Period

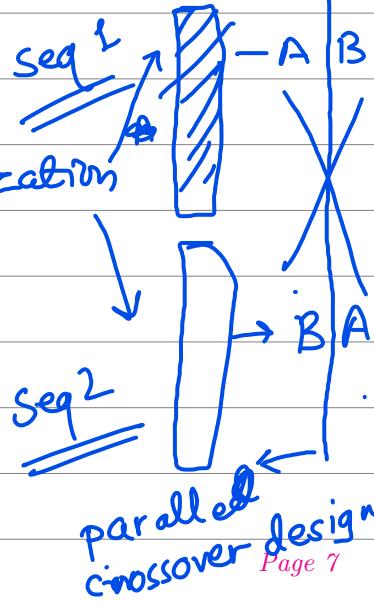
inclusion &
exclusion
criteria

Titration
design



+ training
+ placebo
+ compliance

Randomization



parallel
crossover design

?

Titration design - ①

②

③

④

⑤

⑥

Upward

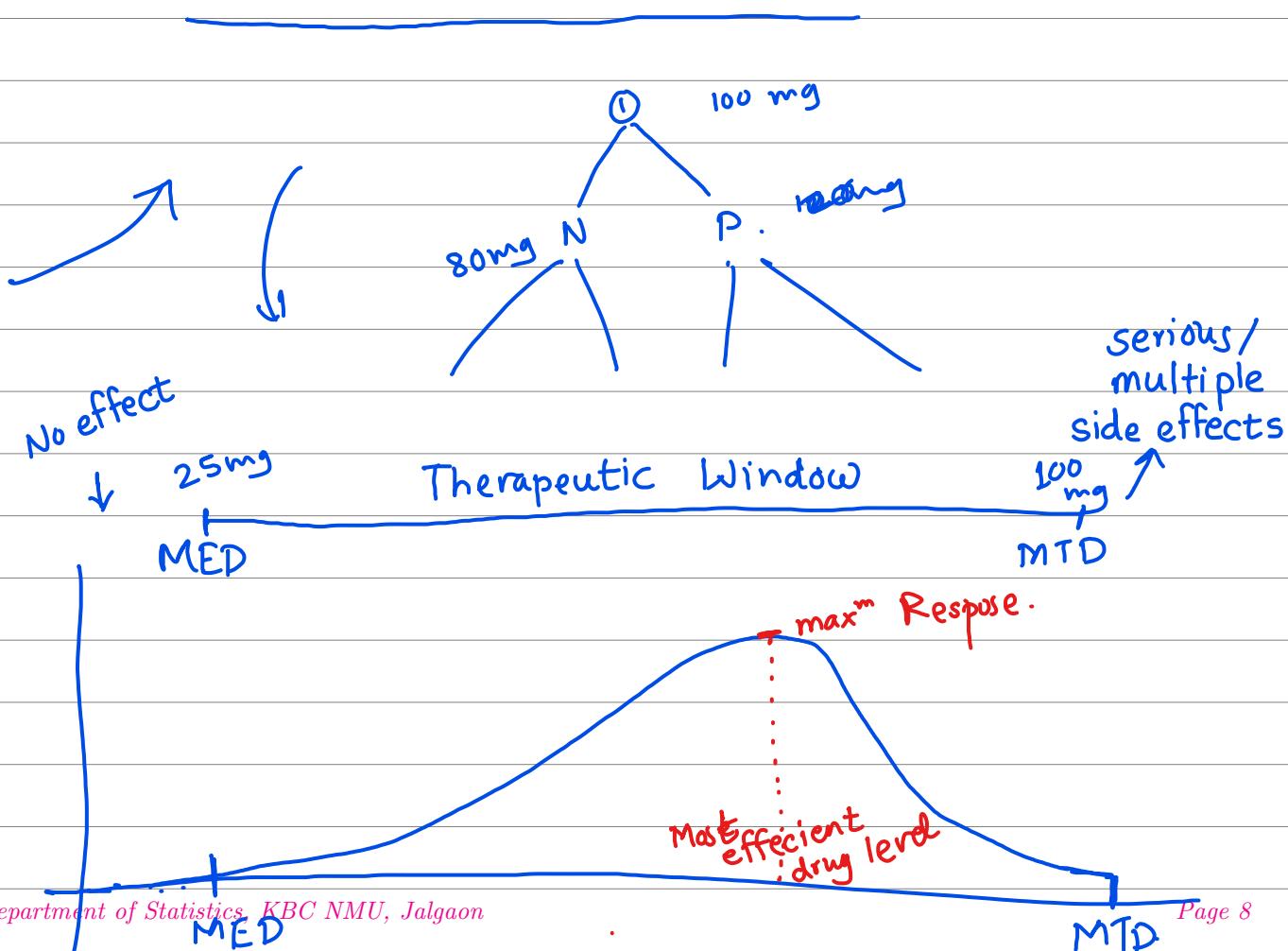
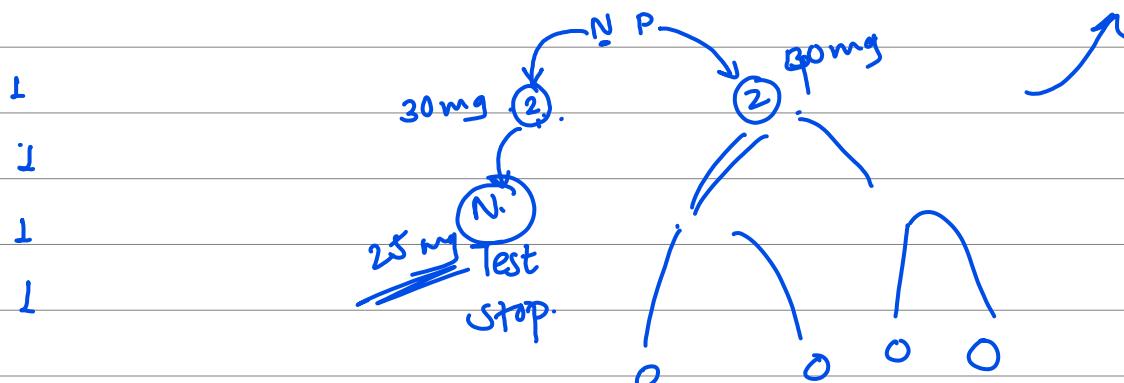
Upward-downward

downward

Human

Safety

①. 30mg -



① Methods of blinding

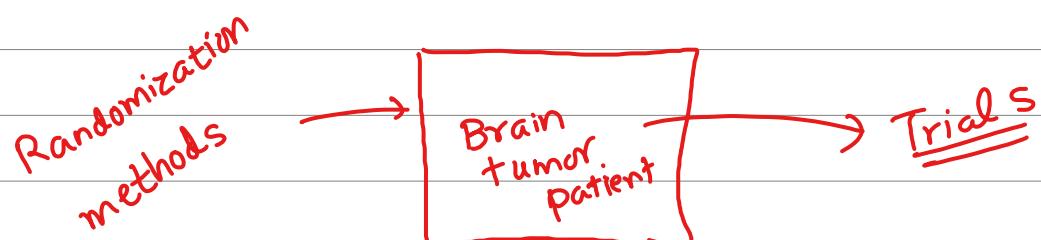
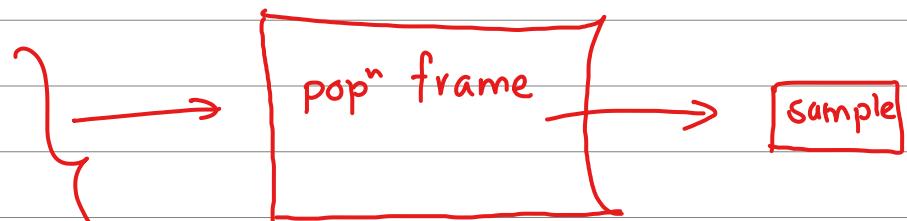
- open label** ① No - Everyone knows
- ② Single - Patient / Dr. any one is blinded
- ③ Double - & no one knows the allocations
- ④ Triple - Patient / Dr / Other staff all are blinded
↳ Data collectors - Nurse

Data Analysts - Statisticians

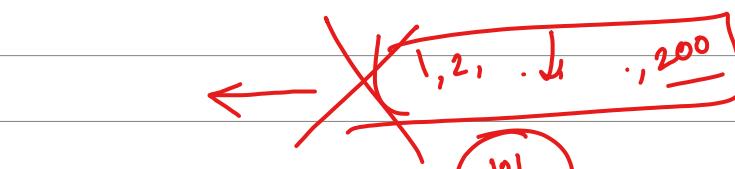


* Randomization ✓

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



Randomization
Assignment of patients to treatment groups

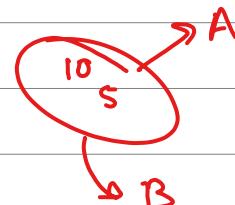


Randomization
Assignment of patients to treatment groups

Bernoulli (0.5)

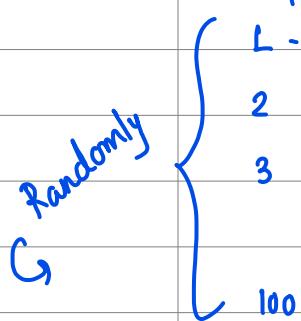
1	2	3	4	5	6	7	8	9	10
A	B	A	A	B	A	B	B	A	

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



① Complete Randomization

drugs
A & B assign with equal prob.

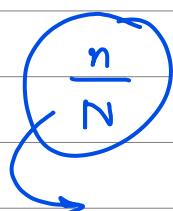


using R → SRSWR

① sample

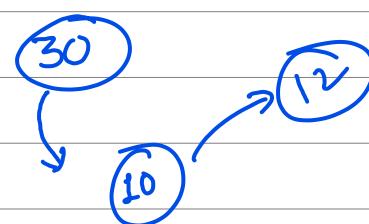
② Bernoulli: — $0.5 \rightarrow L \rightarrow A$
 $0 \rightarrow B$

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?

100 10

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

Randomization

100,000
100 → Treatment

① Patient Popn → ^{Random} 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 ✓

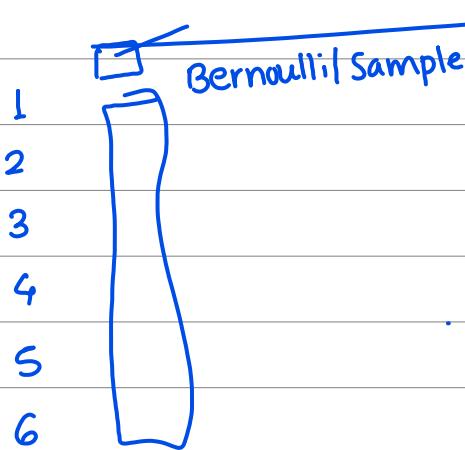
A 1 4 6 ✓ $n(A) = 3$

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

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

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

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

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

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

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

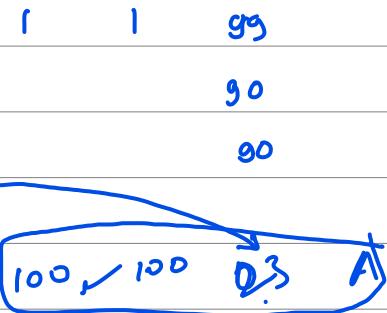
30 patients divided into 3 blocks

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

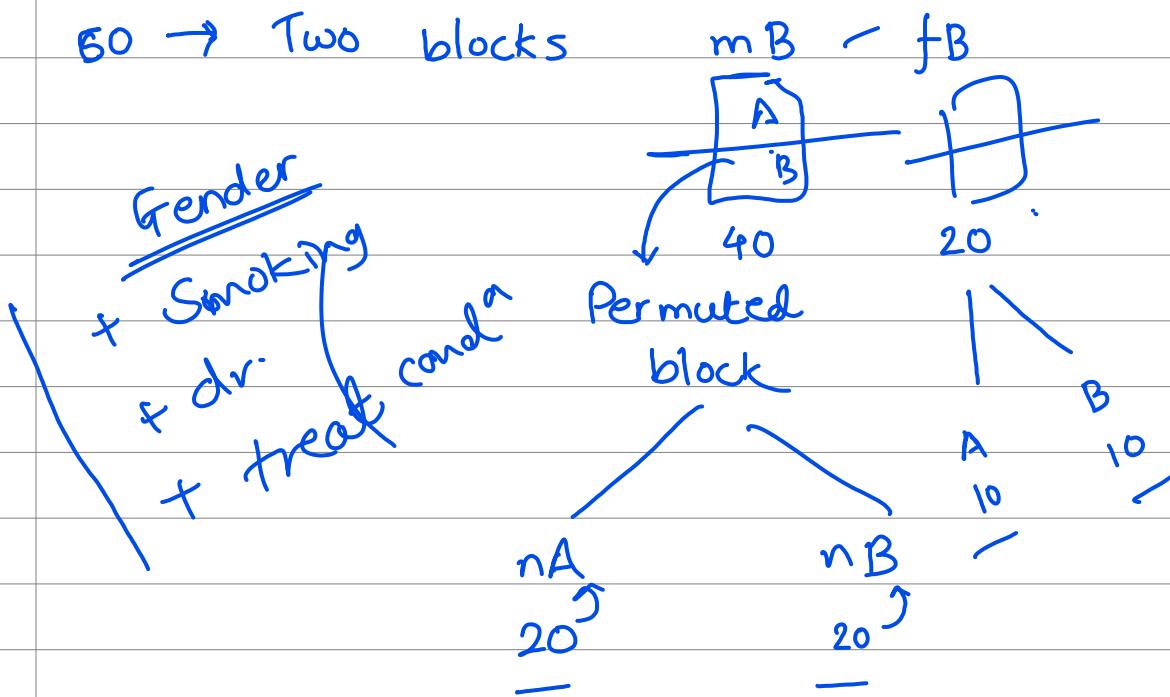
Adaptive Randomizations

① Treatment Adaptive Randomization

② Covariate A R

(Stratified Randomization)

③ Response A R



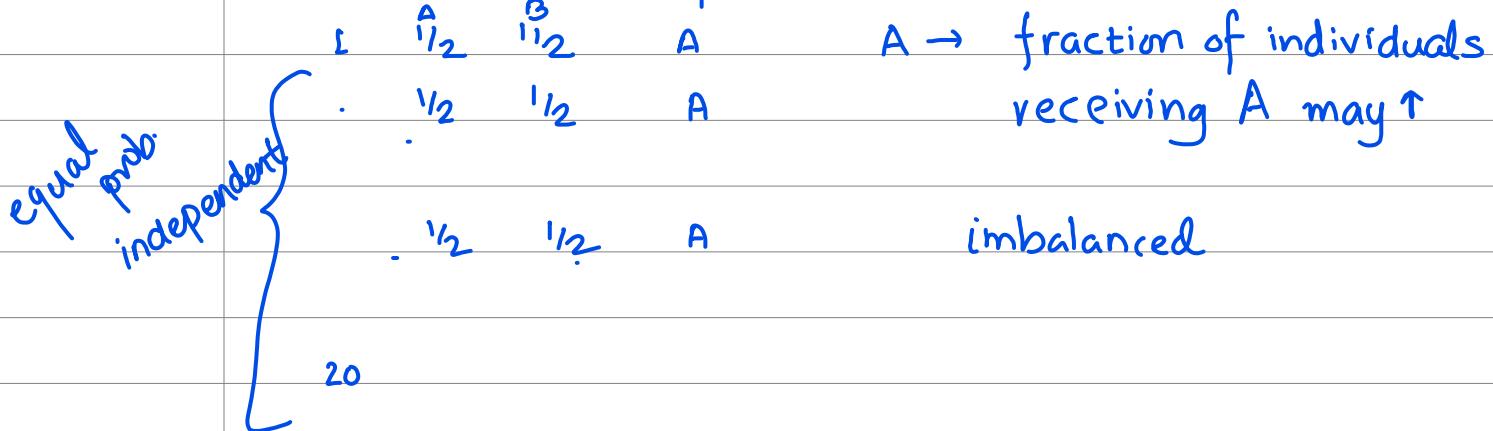
* Covariate :- Strata \rightarrow Covariate - Seq's -

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

Covariate - Groups - ✓ Permutated

Complete - Randomiz. 4 - NM

* Treatment Adaptive Randomization



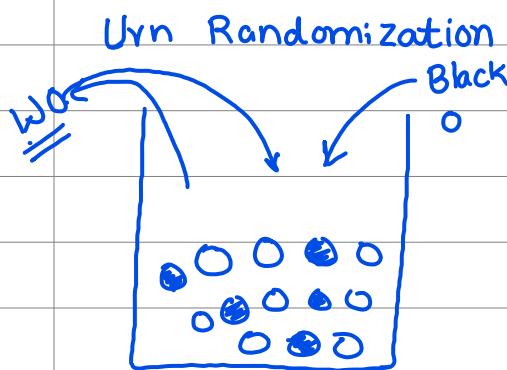
Efron (1971)

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')

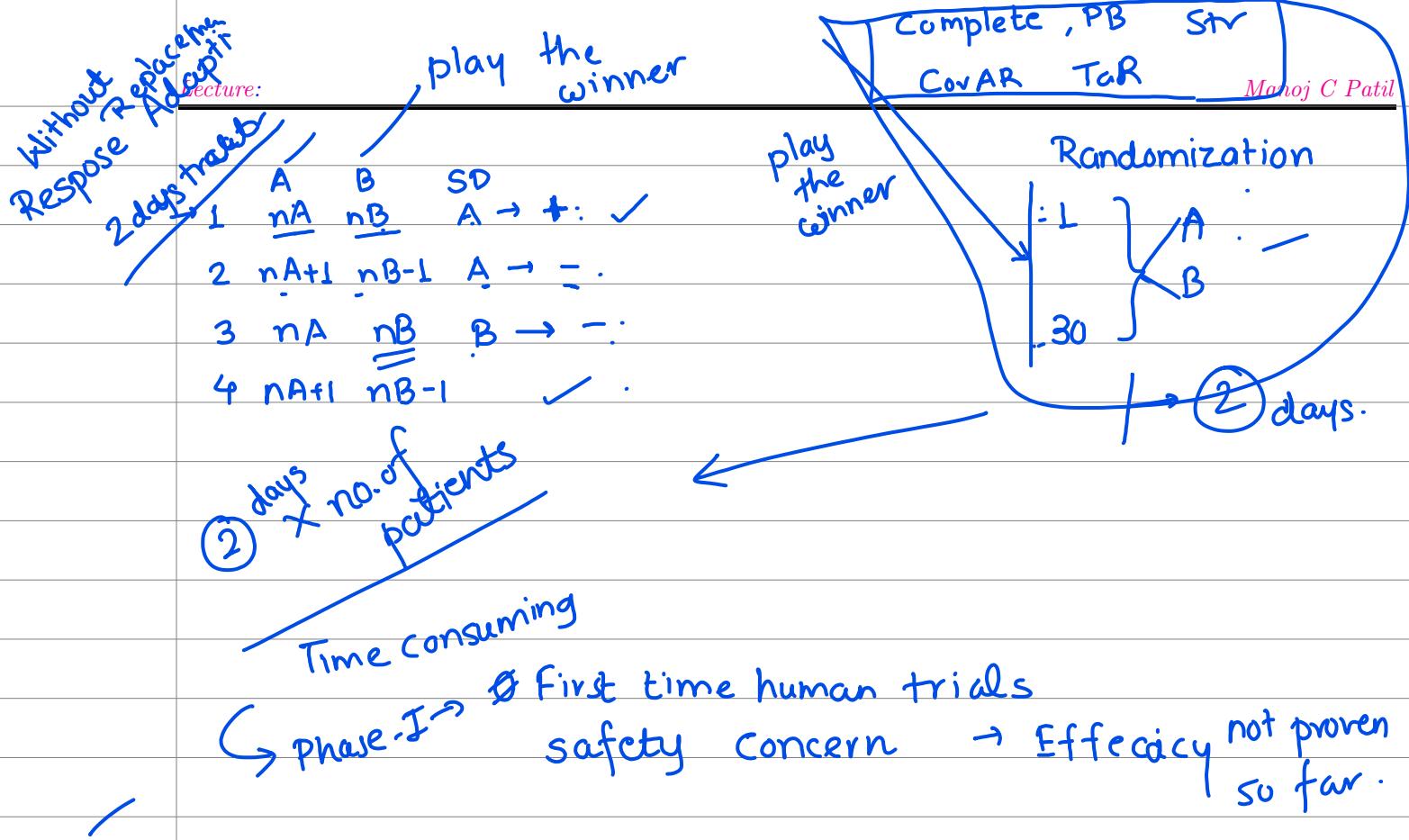
tre[1] =

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

```

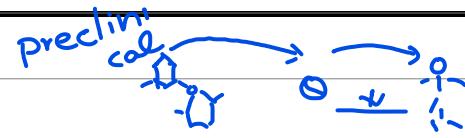
for (i=2:30){
  if(tre[i-1] == 'T') {nB=nB+1} else {nW=nW+1}
  tre[i] = Samp
}
  
```

* Response Adaptive Randomization
(Play the winner -)



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

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

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

II

First time - well controlled CT. ① Effectiveness - ② Dose-Response Rel*
- Dose Range

100-1000 II A
several hundreds subjects

II B

several thousands ✓ extended phase II trials - Effectiveness

III

controlled & uncontrolled trials

Physicians Label

several thousands

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

⇒ Drug Approval Process

Submission

Trials → Phase III B ✓

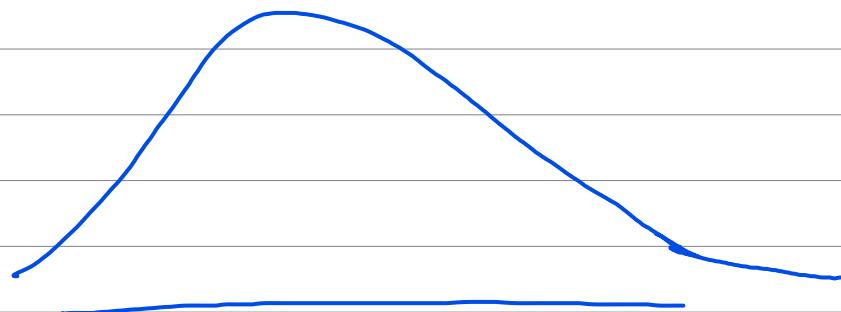
IV

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
therapeutic window

2 side
lower
1.
Same

MED Therapeutic window MTD

* Control ? ∵ Treatment

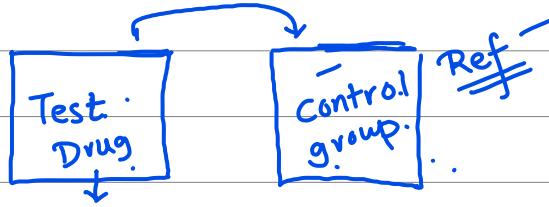
Ref: ① No treatment

② Placebo treatment

③ Active Drug

④ Dose-response concurrent

⑤ Historical concurrent



Drug is effective

(Therapeutic window) concurrent control

↑
Test

parac.

Rare disease :-

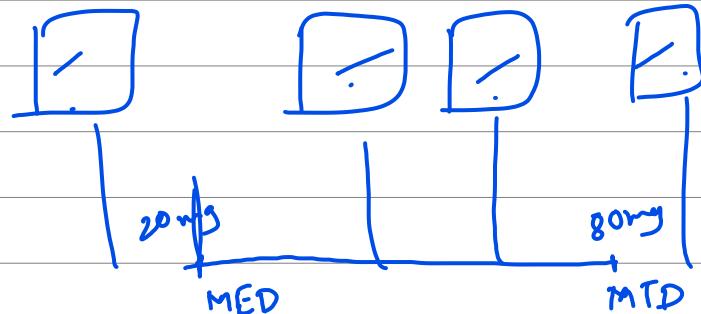
e.g. Brain tumor :-
10-12 patient



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

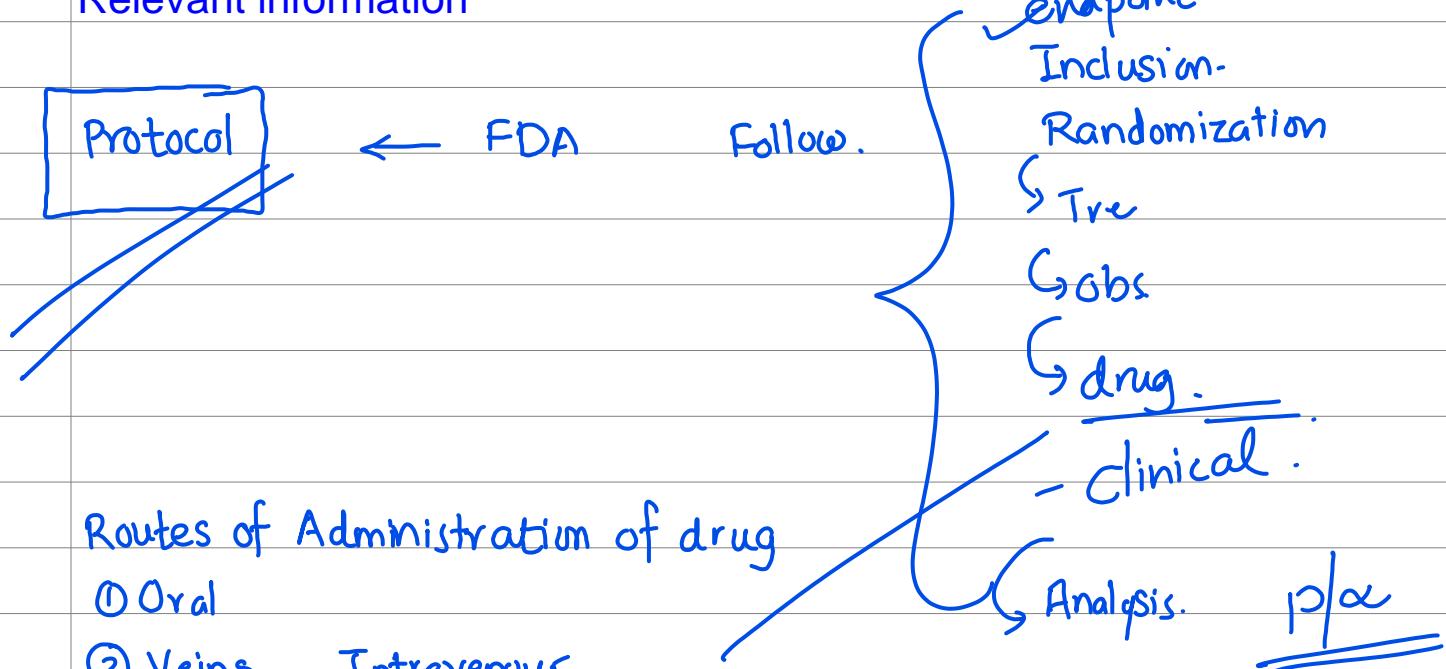
* Govt Health dept

* 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



Center 14 Test 01 Sub 001

1401001
1502009
= = =

Labelling

- potential bias

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

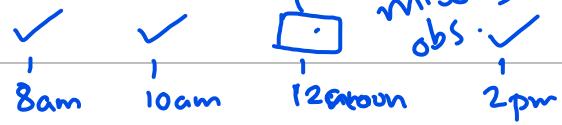
Ref

+ Milk ✓
 + Drug B ✓

① Dropouts ? Treatment →

who fails to complete

② missing value



③ gmat Premature Termination.

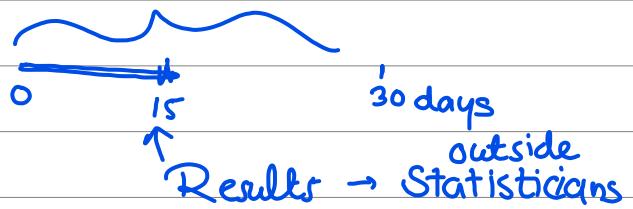


* Multicenter Trials :- ?

① No. of pat subjects ↑

② Results generalizable

* Interim Analysis

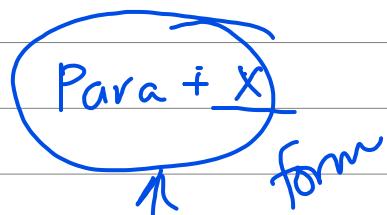


Absent.'r

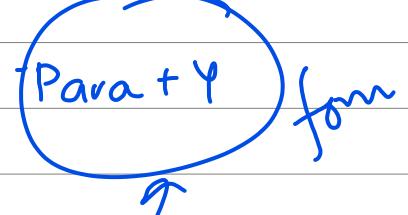
2001, 4, 6, 12, 14, 16, 17, 18, 22, 25, 33, 34, 35, 43, 44, 45, 47, 50, 54, 55

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.

