

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

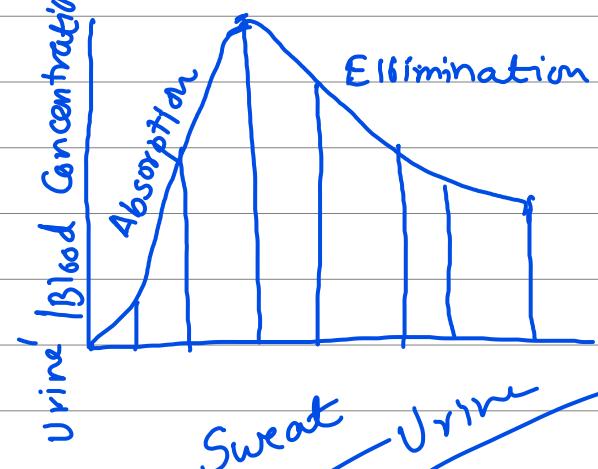
Pharmacology

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 800 - 1000

\rightarrow Thousands

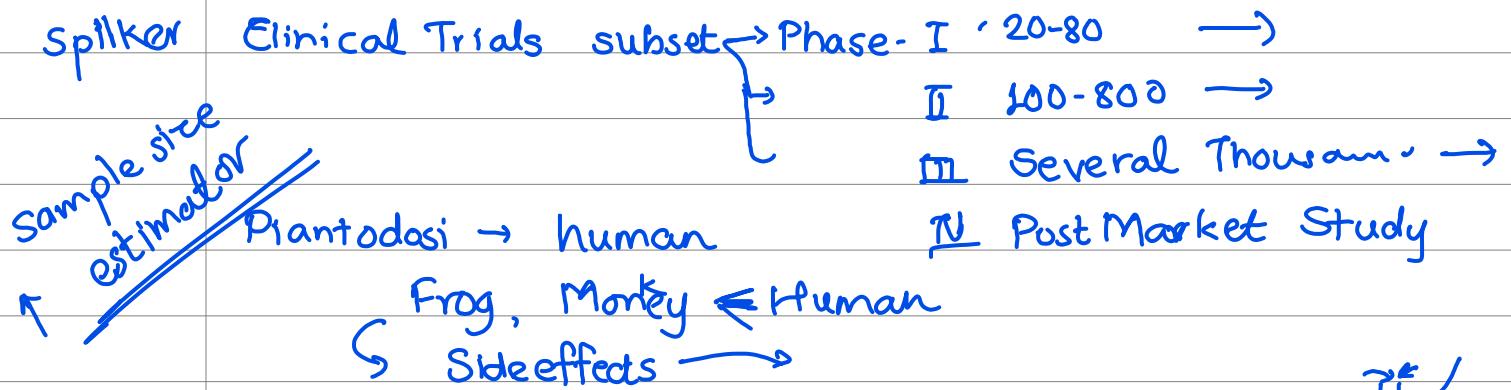
\rightarrow Post Market Analysis

side effects \rightarrow min

effectiveness \rightarrow side effect

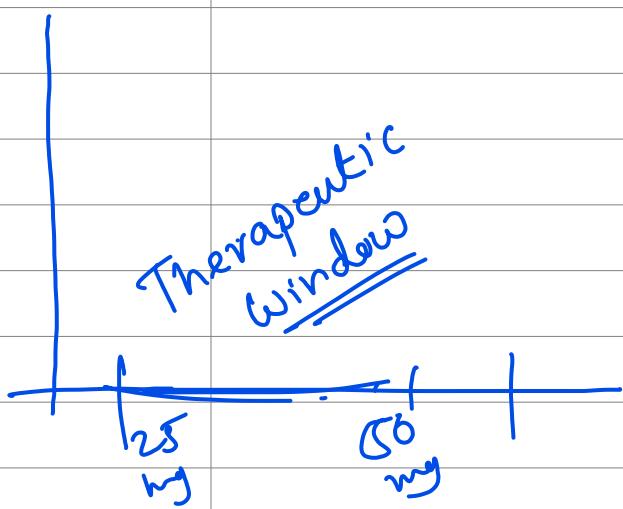
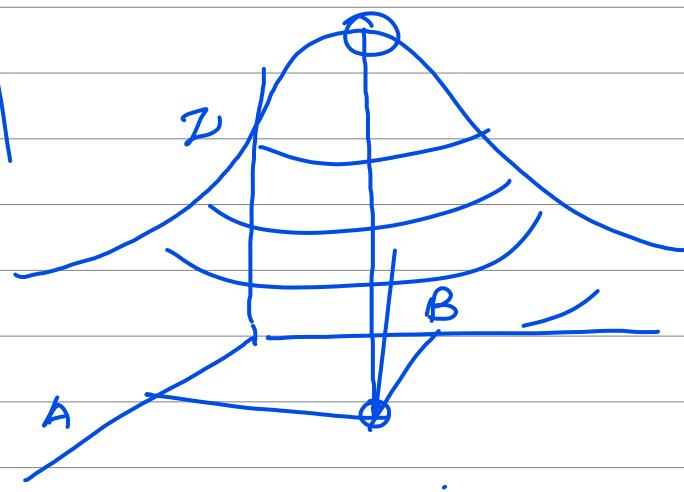
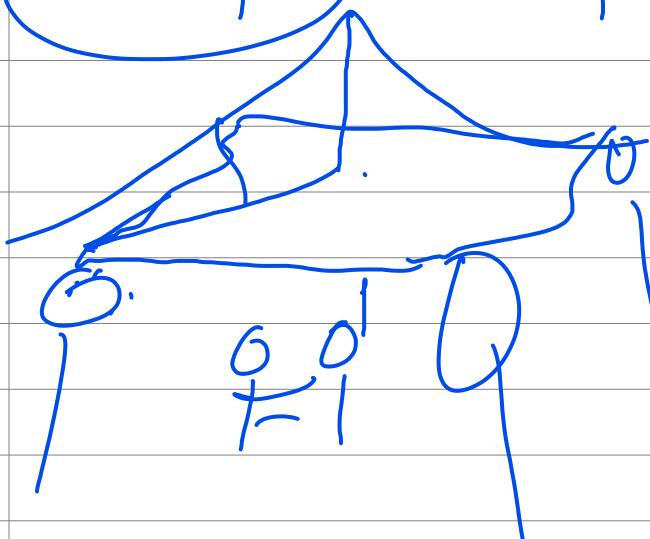
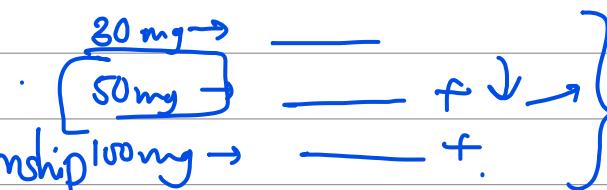
Thousands \rightarrow Physicians labelling

Life threatening side effects



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 ?

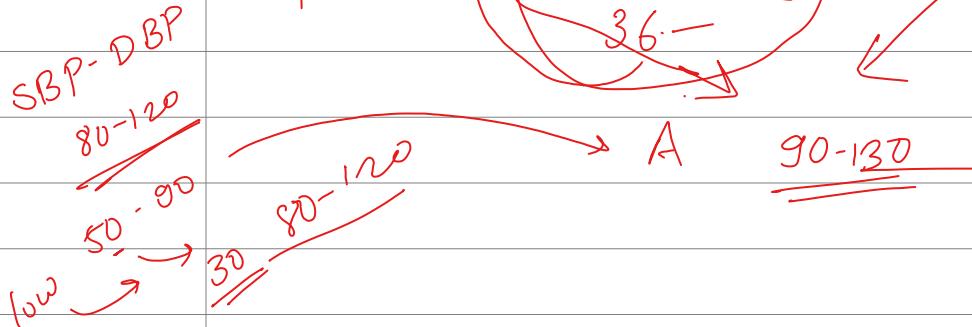
UST - LSL

36 -

Clinical diff

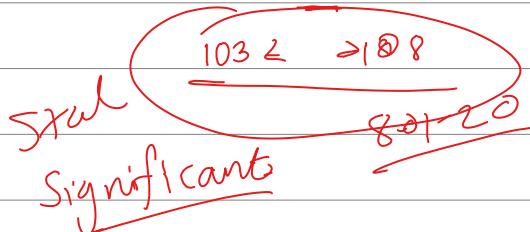
LSL ? USL ?

Clinician / Doctors



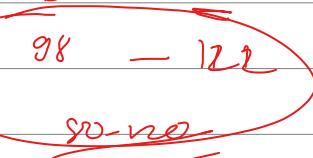
$$A \rightarrow \mu_A = 105$$

$$\delta_A = 1$$

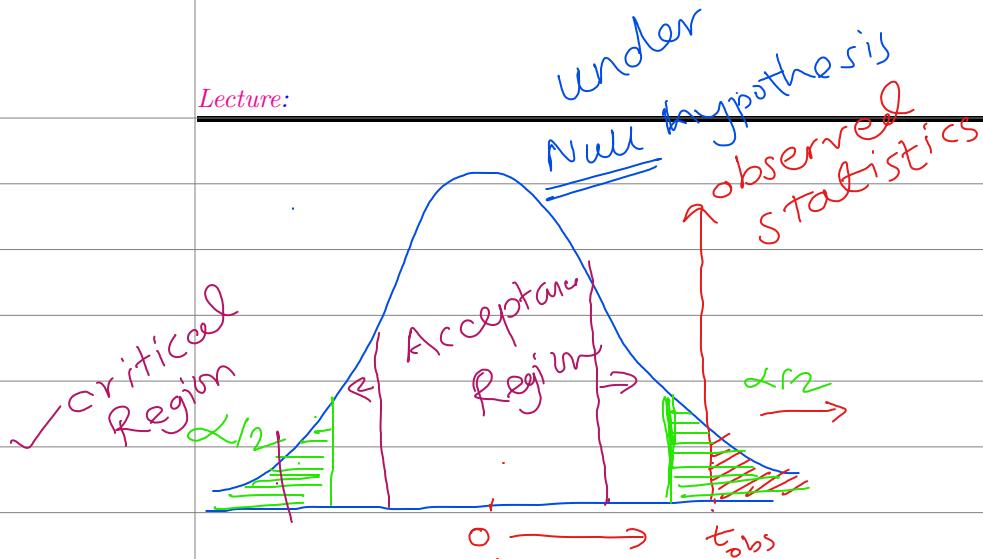


$$\beta = \mu_B = 110$$

$$\delta_B = 2$$



Clinician



$$\alpha > p$$

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

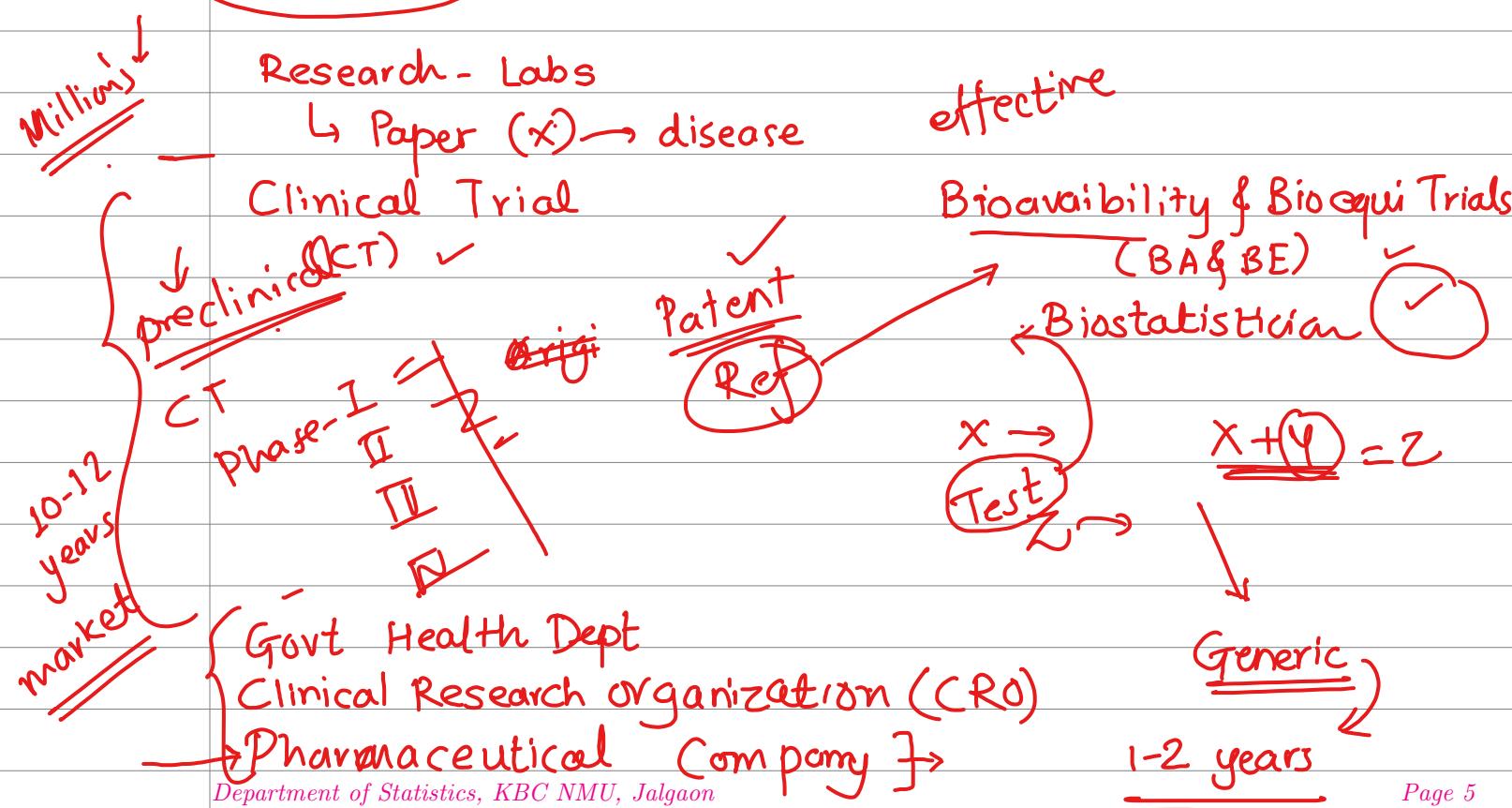
$p > \alpha \Rightarrow \text{fail to}$

$\text{Reject } H_0$

~~Confusion~~
~~Rohan Sir~~

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

One way $H_0: \frac{\underline{\bar{x}} \geq \underline{\mu_0}}{\underline{\bar{x}} < \underline{\mu_0}} \Rightarrow \begin{cases} 1 - \text{CDF} \\ \text{CDF} \end{cases}$



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

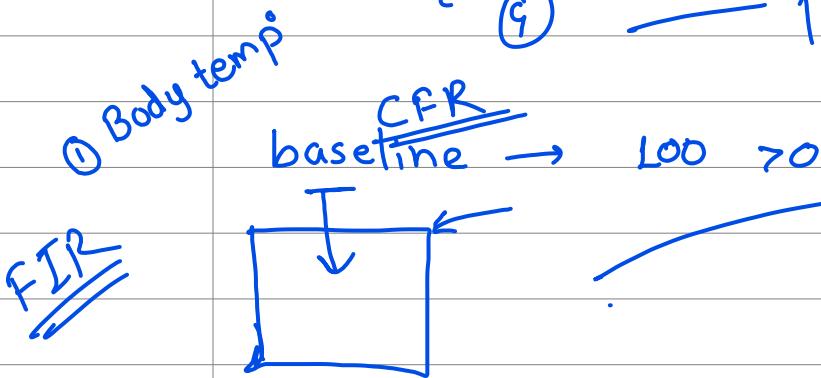
- ① Treatment to reduce weight
- ② Immunity
- ③ Muscles

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

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

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

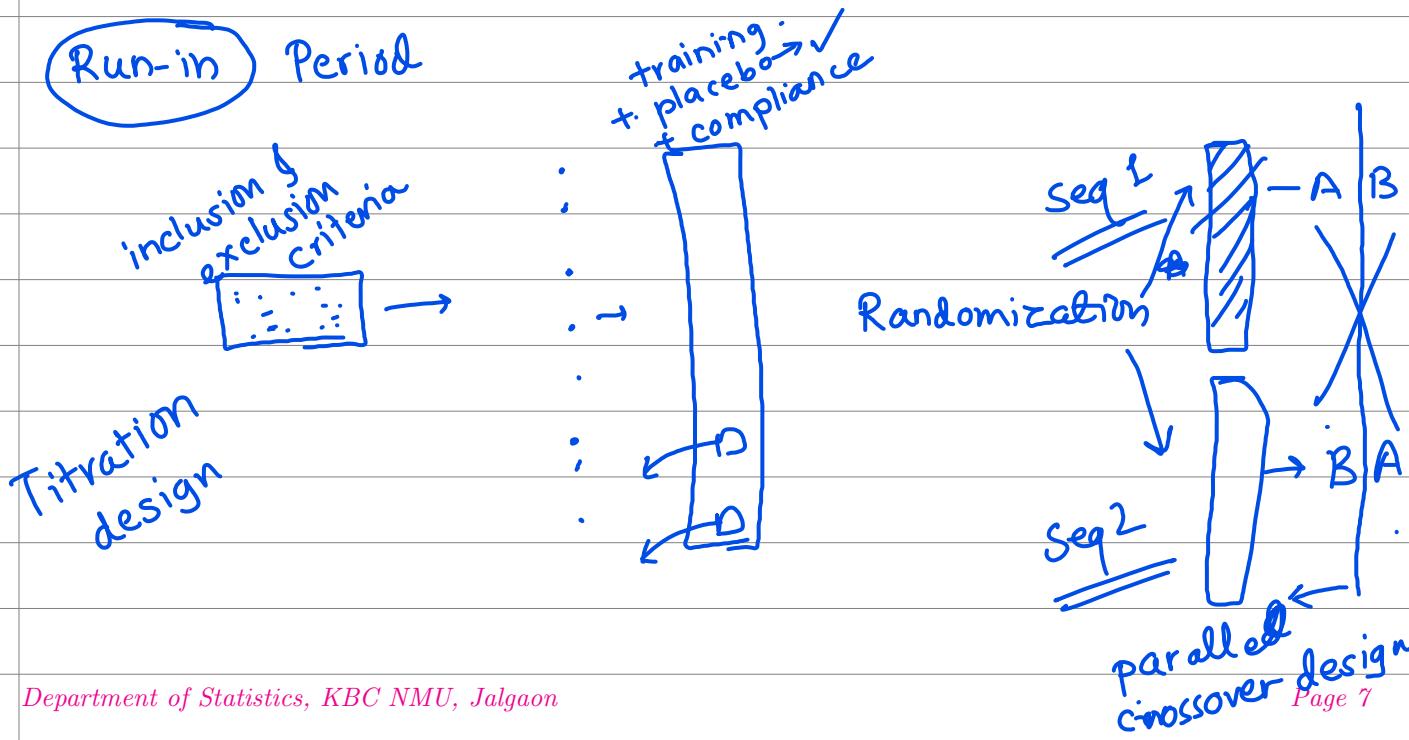
Inclusion & Exclusion

- ① < 18 & > 60 years old age Exclude
- ② Feeding mother / pregnant
- ③ History disease Medications
- ④ _____
- ⑤ _____

Inclusion
Some

- ✓ ① Disease
- ✓ ② Healthy volunteer
- ③ > 18
- ④ _____
- ✗ ⑤ _____

Some inclusion & all exclusion criteria
follow
not followed



?

Titration design - ①

②

③

④

⑤

⑥

Upward

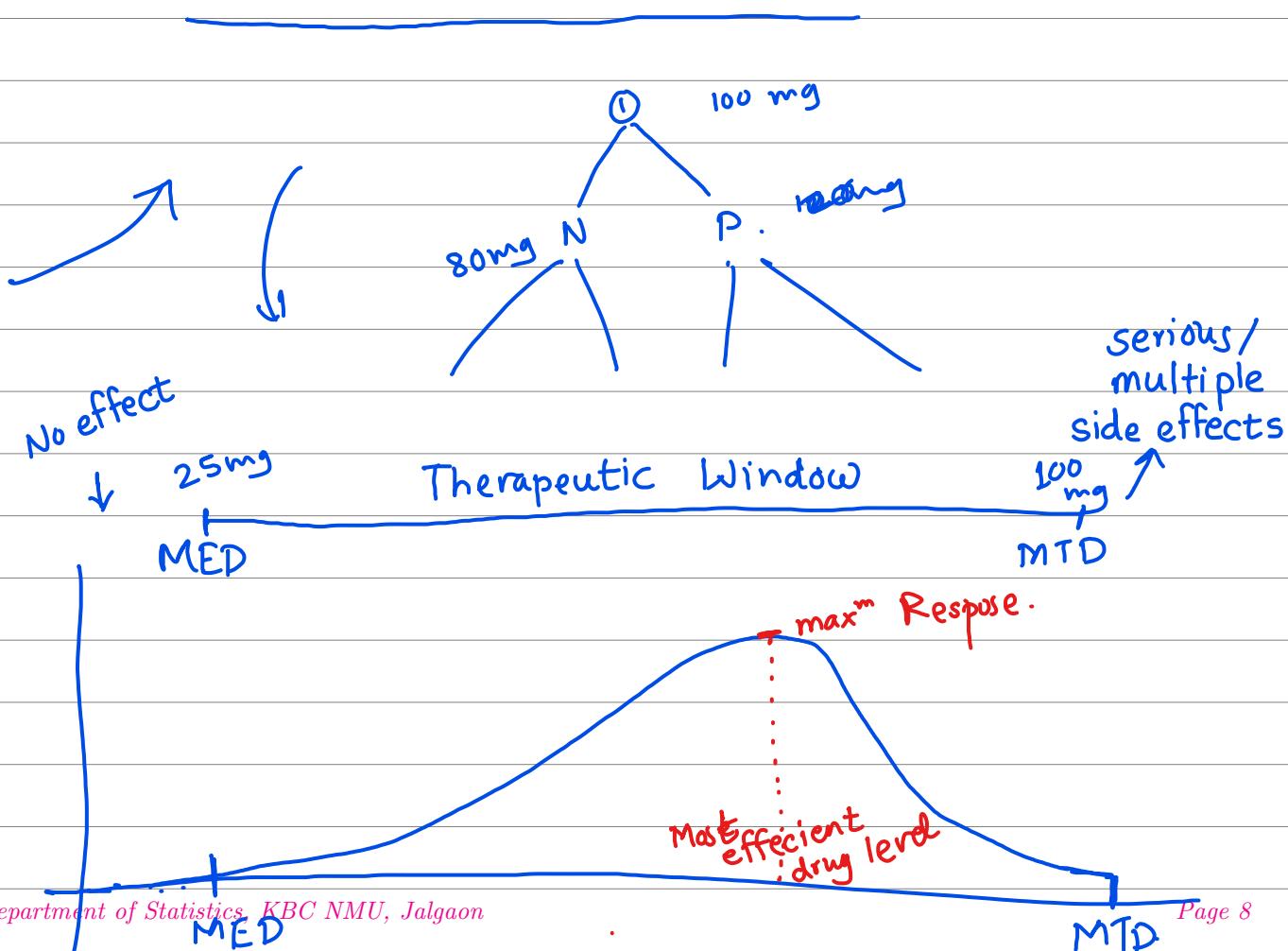
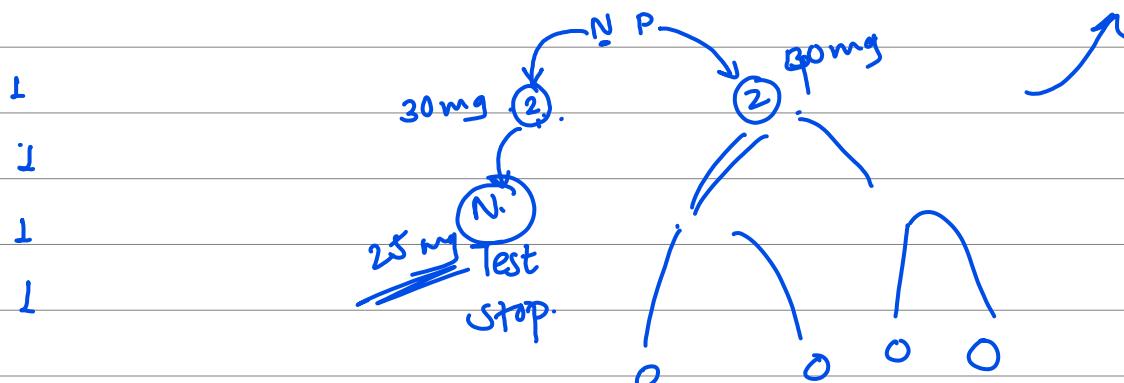
Upward-downward

downward

Human

Safety

① . 30mg -



① Methods of blinding

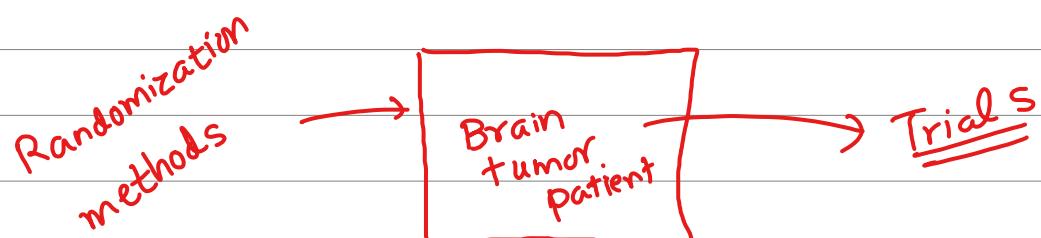
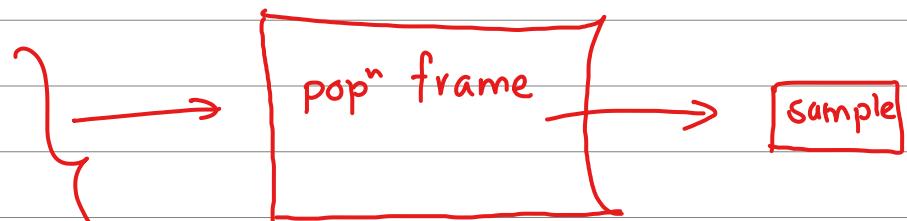
- open label** ① No - Everyone knows
- ② Single - Patient / Dr. any one is blinded
- ③ Double - & no one knows the allocations
- ④ Triple - Patient / Dr / Other staff all are blinded
↳ Data collectors - Nurse

Data Analysts - Statisticians

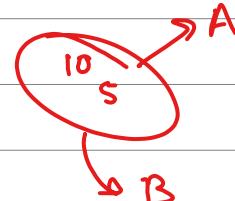
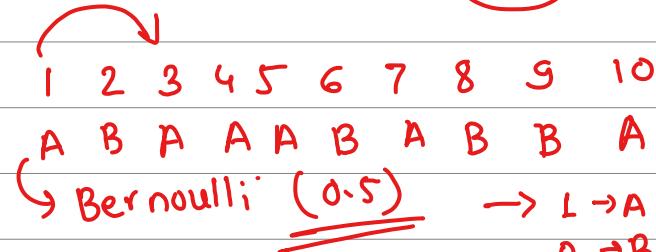
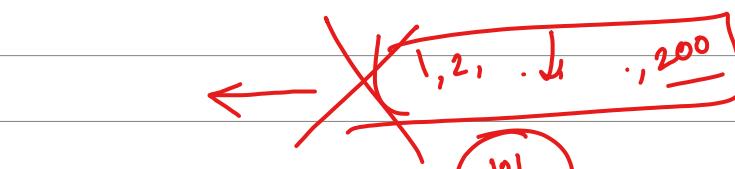


* Randomization ✓

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

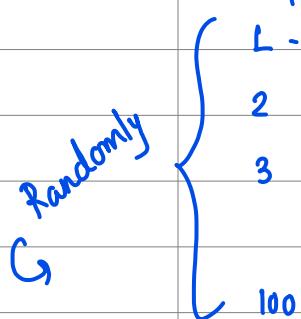


Randomization
Assignment of patients to treatment groups



① Complete Randomization

drugs
A & B assign with equal prob.

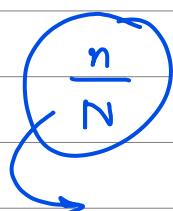


using R → SRSWR

① sample

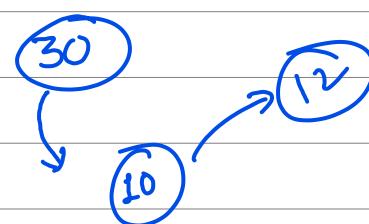
② Bernoulli: — $0.5 \rightarrow L \rightarrow A$
 $0 \rightarrow B$

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 → ^{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 ✓

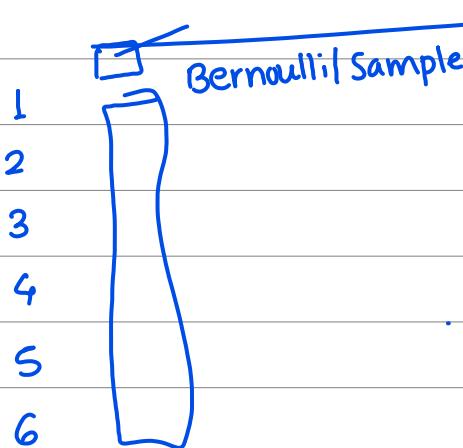
A 1 4 6 ✓ $n(A) = 3$

B 2 3 5 ✓ $n(B) = 3$

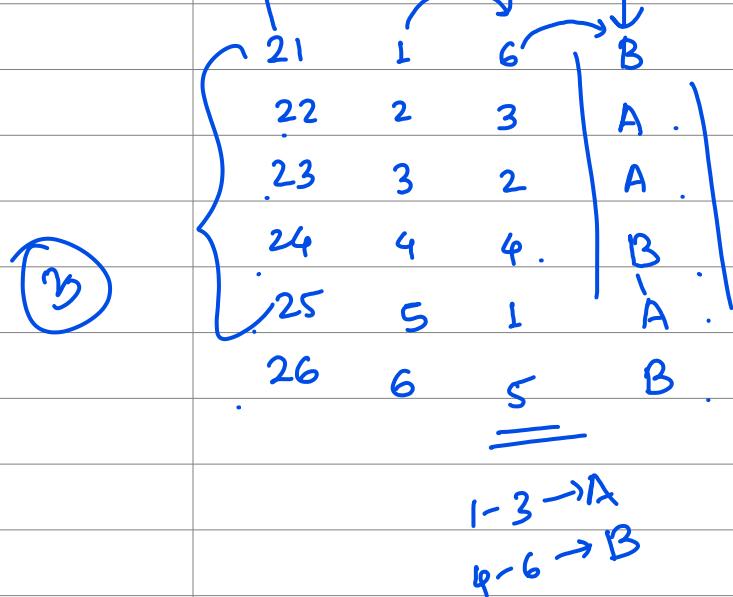
$(1 \ 2 \ 3 \ 4 \ 5 \ 6) \rightarrow$ Random Sample without replace
A A A

3 2 5 1, 4 6

A A B A B B



| | | |
|---|---|---|
| | A | B |
| 1 | A | A |
| 2 | A | A |
| 3 | A | B |
| 4 | B | A |
| 5 | B | A |
| 6 | B | 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 | 9 | 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 | | | | |
| | | | | | |
| | | | | | |

$n_A = 15$
 $n_B = 15$

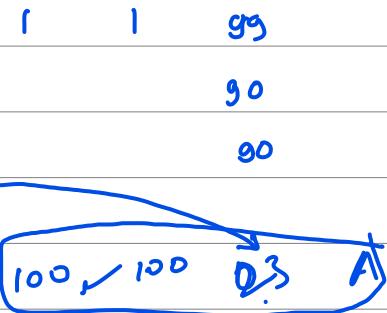
$\frac{15}{15} \quad \frac{30}{15}$

$\frac{8-A}{T-B} \quad \frac{7-B}{8-B}$

$5 \rightarrow A$
 $5 \rightarrow B$

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

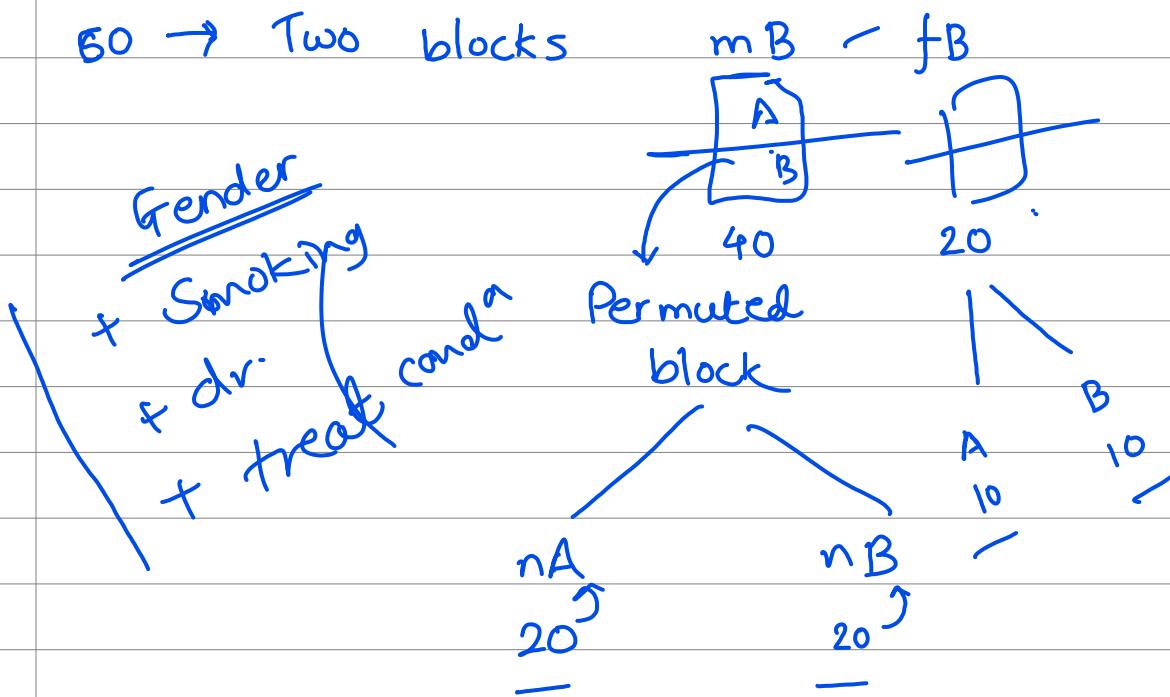
Adaptive Randomizations

① Treatment Adaptive Randomization

② Covariate A R

(Stratified Randomization)

③ Response A R



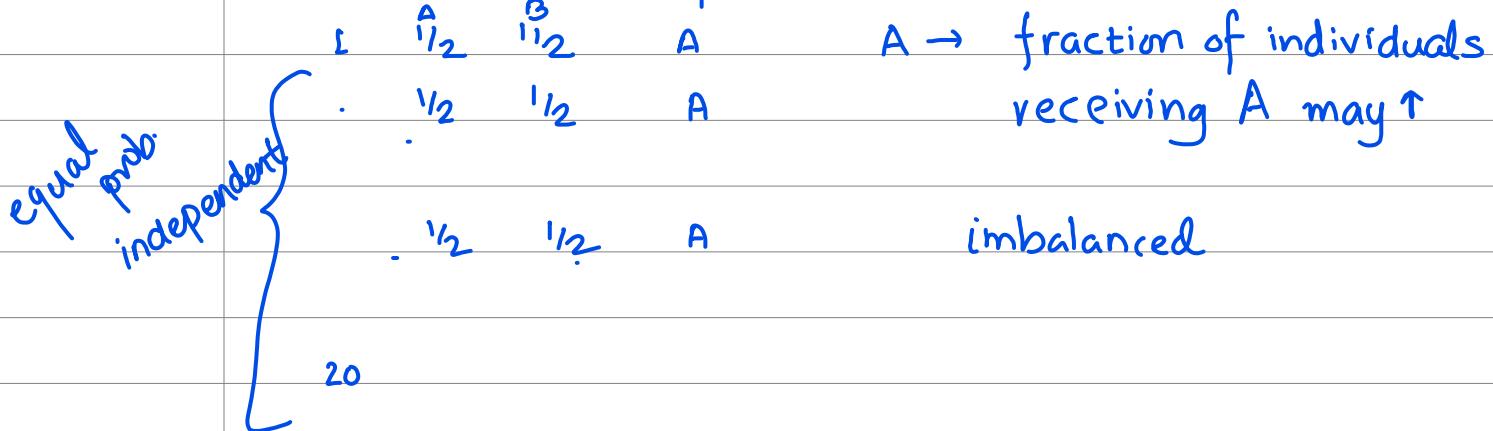
* Covariate :- Strata \rightarrow Covariate - Seq's -

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

Covariate - Groups - ✓ Permutated

Complete - Randomiz. 4 - NM

* Treatment Adaptive Randomization



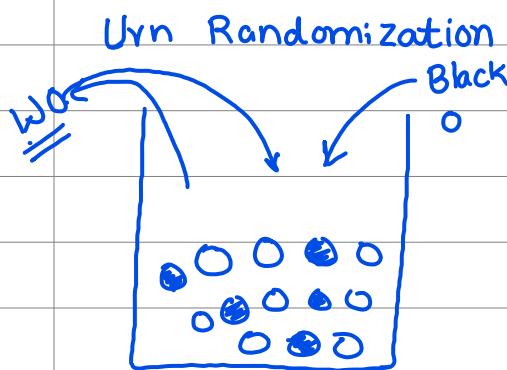
Efron (1971)

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')

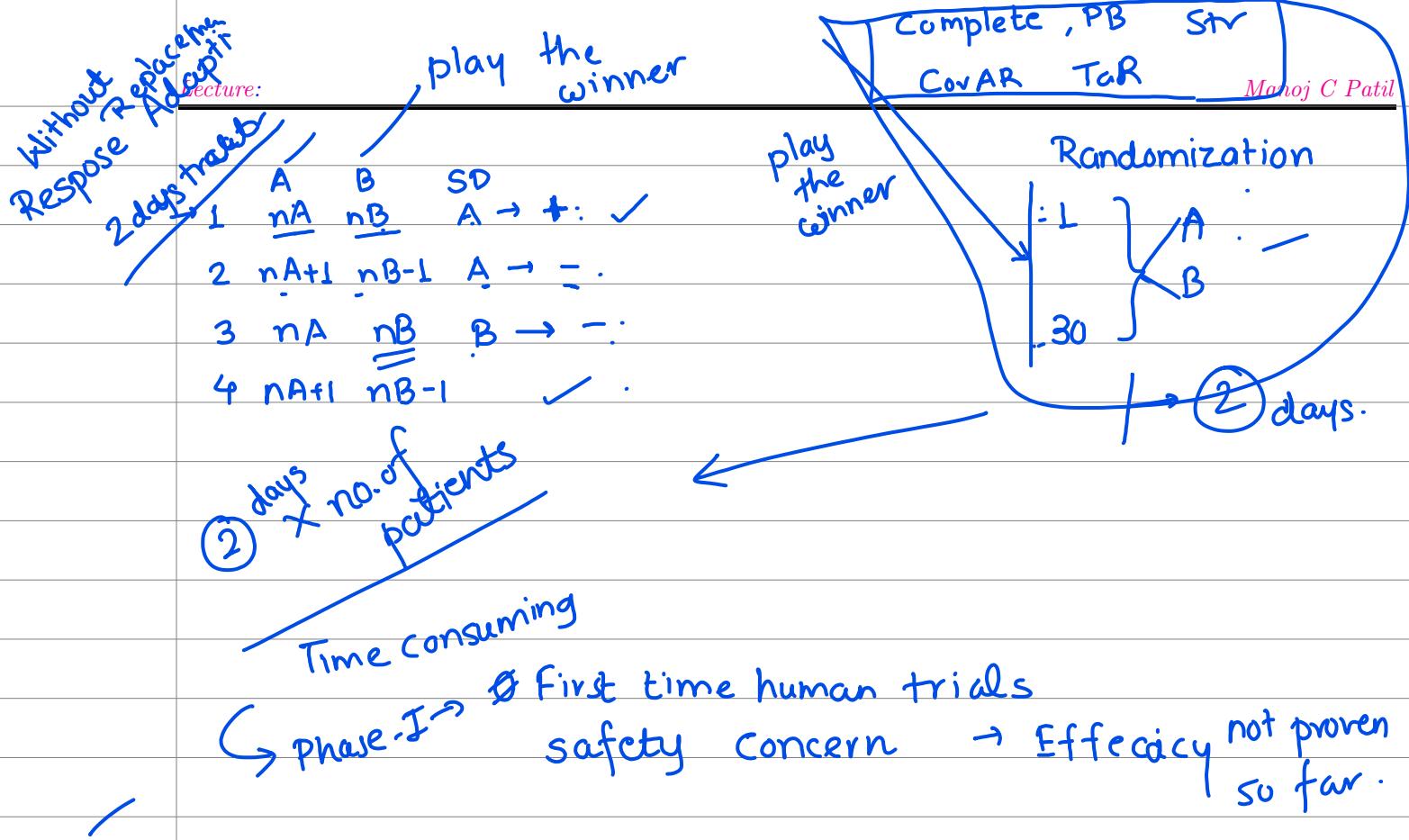
tre[1] =

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

```

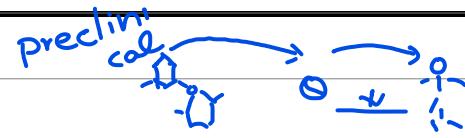
for (i=2:30){
  if(tre[i-1] == 'T') {nB=nB+1} else {nW=nW+1}
  tre[i] = Samp
}
  
```

* Response Adaptive Randomization
(Play the winner -)



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.

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



Phases- clinical trials

I
mostly healthy
20-80 subjects

II

100-1000
several hundreds subjects

II A

several thousands ✓

II B

several thousands ✓ extended phase II trials - Effectiveness

III

controlled & uncontrolled trials

Physicians Label

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

⇒ Drug Approval & Process Submission
Trials → Phase III B ✓

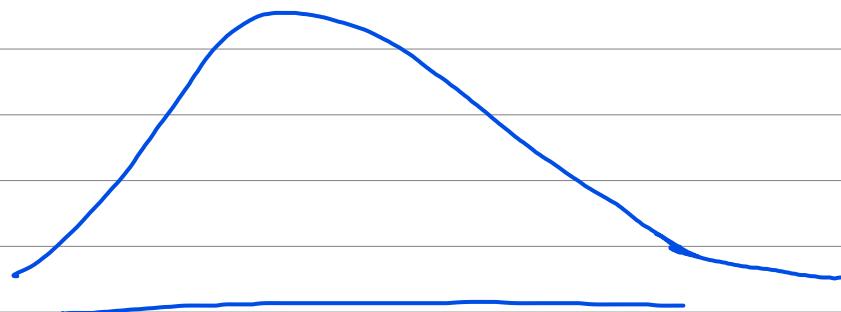
IV

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

2 side
lower
Same

MED Therapeutic window MTD

* Control ? ∵ Treatment

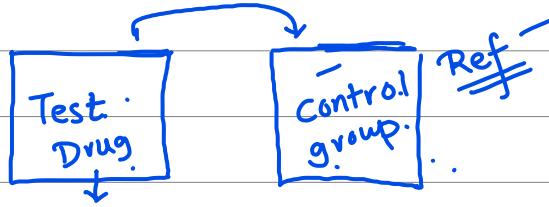
Ref: ① No treatment

② Placebo treatment

✓ ③ Active Drug

④ Dose-response concurrent

⑤ Historical concurrent



Drug is effective

(Therapeutic window) concurrent control

↑
Test

parac.

Rare disease :-

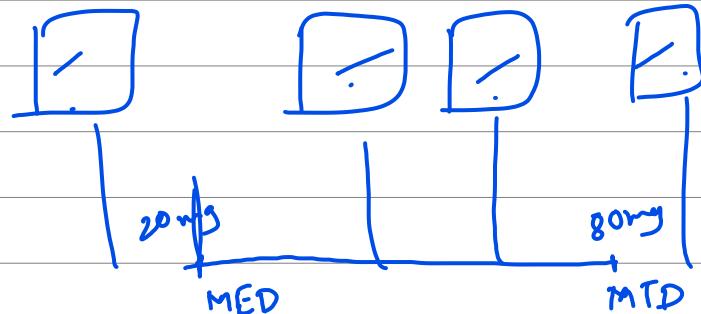
e.g. Brain tumor :-
10-12 patient



No. patient



1985
assume =



* 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

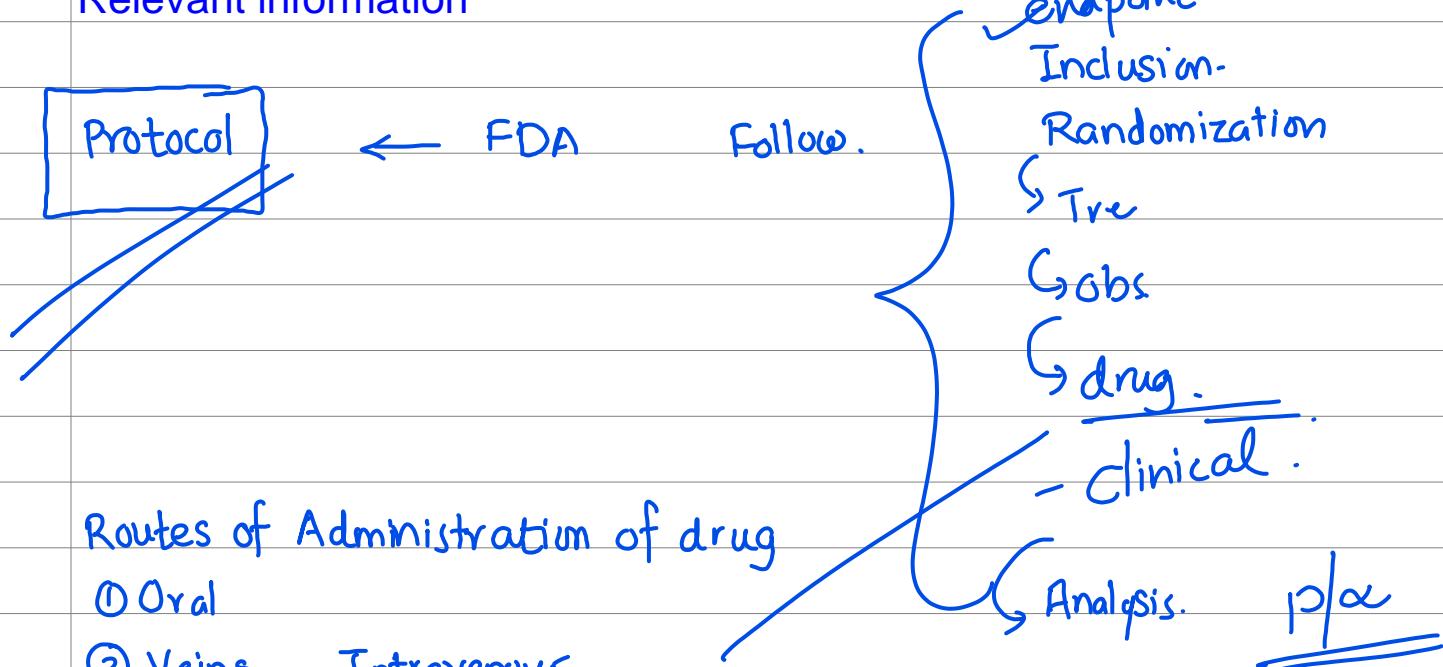
* Govt Health dept

* 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. ✓

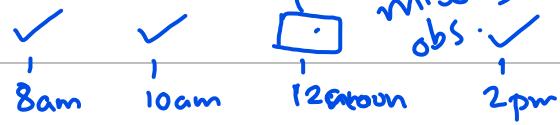
Ref

+ Milk ✓
 + Drug B ✓

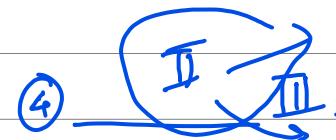
① Dropouts ? Treatment →

who fails to complete

② missing value



③ gmat → Premature Termination.
 ④ 7 pre

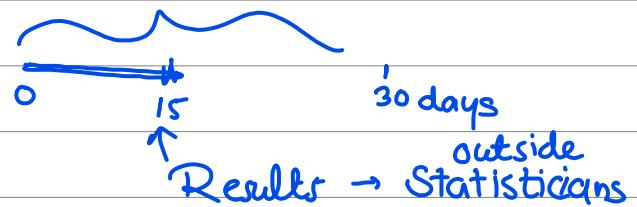


* Multicenter Trials :- ?

① No. of pat subjects ↑

② Results generalizable

* Interim Analysis

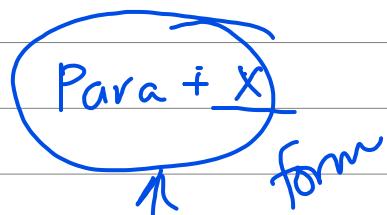


Absent.'r

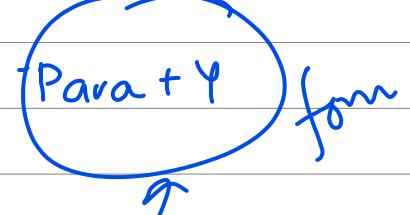
2001, 4, 6, 12, 14, 16, 17, 18, 22, 25, 33, 34, 35, 43, 44, 45, 47, 50, 54, 55

Thank you.
 = 20 students

Patent



Generic. ✓



ANDA
111

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

