

No treatment, Chemo, Radio
 Surgical Procedures

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

US-FDA - Food, Drug, Administration

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

Evaluation

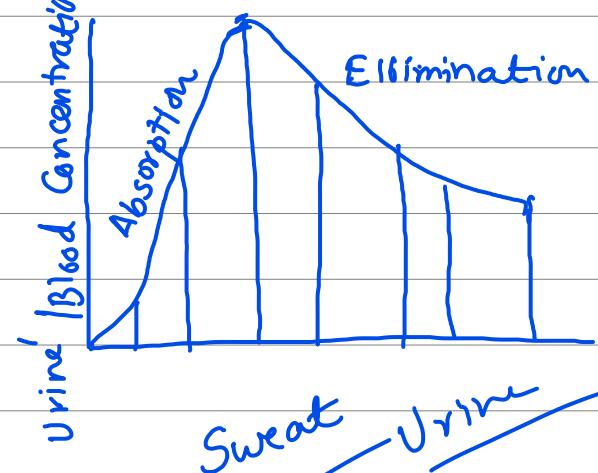
Pharmacology

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

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

Phase-I

\rightarrow 20/80 \rightarrow side effects min

Life threatening side effects

\rightarrow 800 - 1000 \rightarrow effectiveness side effect

\rightarrow Thousands \rightarrow Physicians labelling

= IV Post Market Analysis

Spiller

Clinical Trials subset → Phase- I '20-80 →

Clinical Trials subset → Phase- I '20-80' →
 II 100-800 →
 III Several Thousand →
 IV Post Market Study
 ↗ Plantodasi → human

Sample size estimator Pian

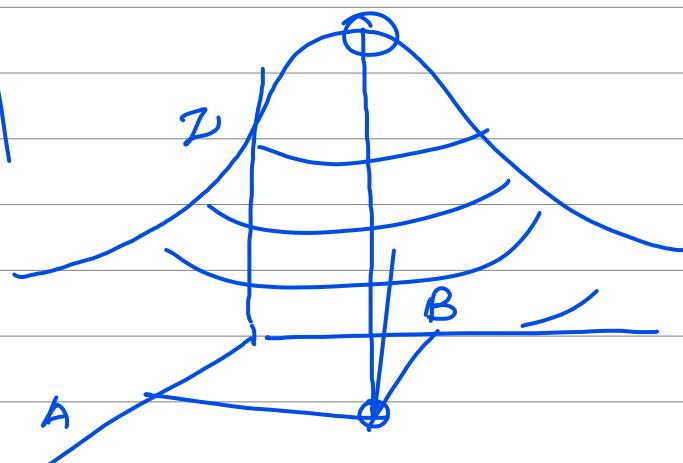
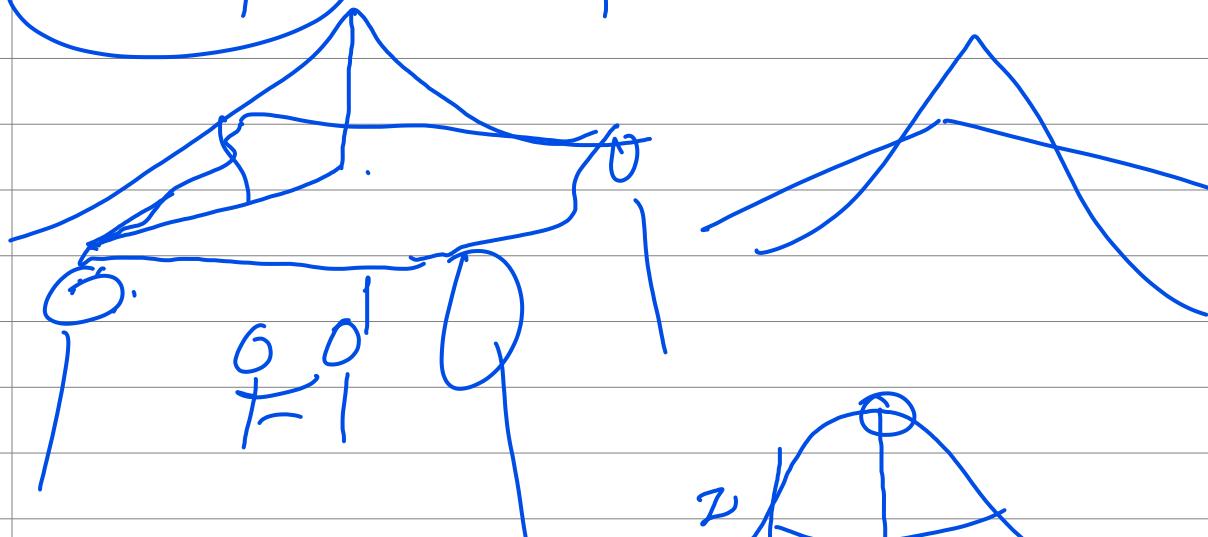
Saw /
st'ime Piantodosi → human

 Frog, Monkey < Human
↓
Side effects

Titration Design

Dose-Response Relation

$$\begin{array}{c}
 30 \text{ mg} \rightarrow \boxed{} \\
 \boxed{50 \text{ mg}} \rightarrow \boxed{} \quad f \downarrow \rightarrow \\
 \text{mship} \ 100 \text{ mg} \rightarrow \boxed{} \quad f.
 \end{array}$$



Therapeutic Window

~~10mg~~
50mg
80mg

MED - Min^m Effective Dose

~~50 mg~~ → MTD → Max^m Tolerable Dose
~~80 mg~~

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 ?

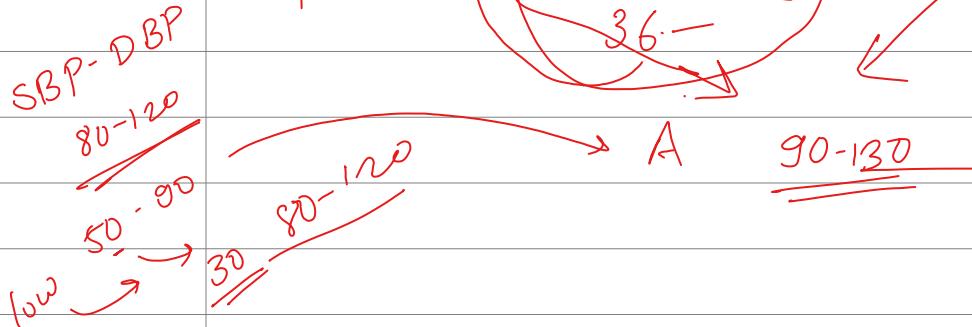
UST - LSL

36 -

Clinical diff

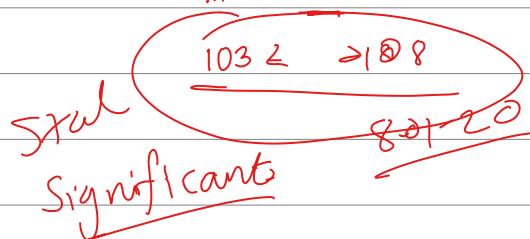
LSL ? USL ?

Clinician / Doctors



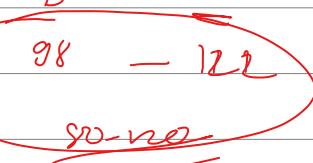
$$A \rightarrow \mu_A = 105$$

$$\delta_A = 1$$

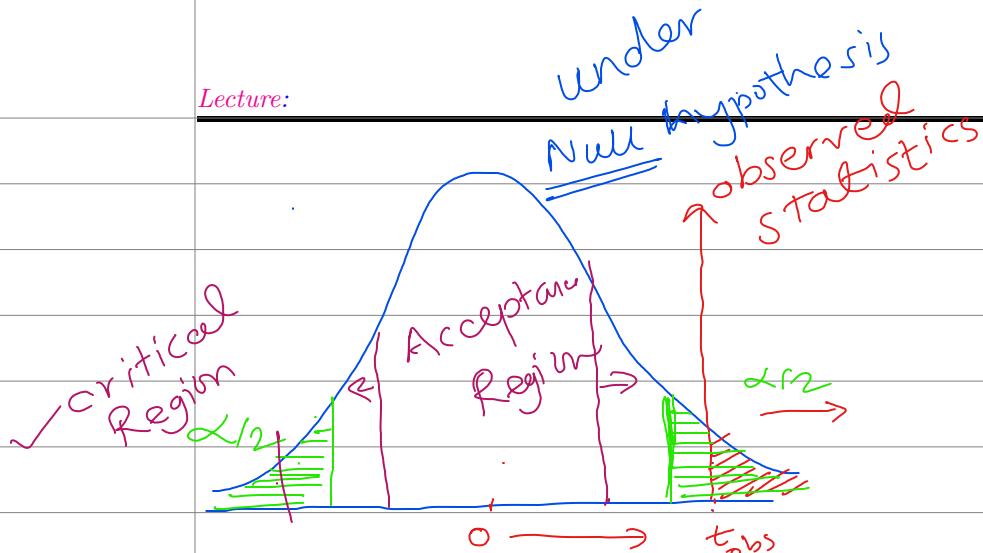


$$\beta = \mu_B = 110$$

$$\delta_B = 2$$



Clinician



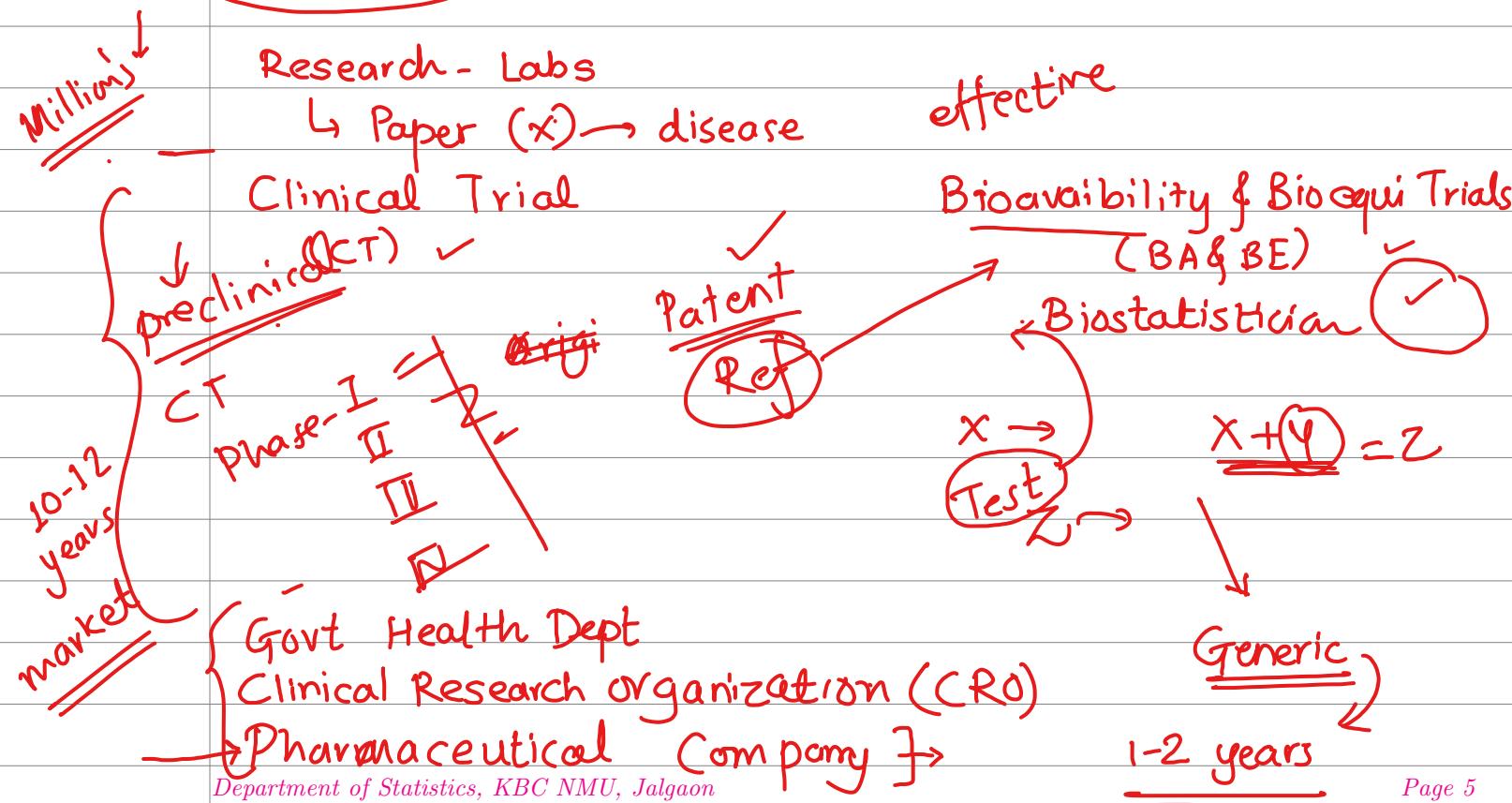
$\alpha > p \rightarrow$ Reject H_0
 $p < \alpha \rightarrow$ Reject H_0
 $p > \alpha \rightarrow$ fail to
 Reject H_0

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) → Generic Drug
 Active ingredient (x)
 Inactive ingre → -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	—	—	—

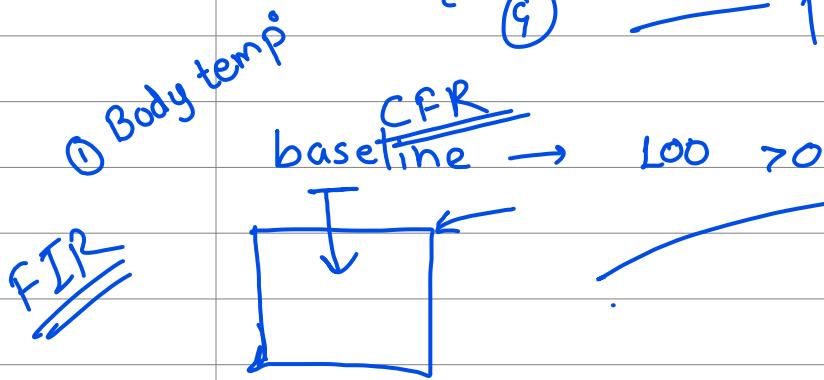
Objectives

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 & ≥ 60 old age Exclude

② Feeding mother / pregnant

③ History disease

Medications

④ _____

⑤ _____

Inclusion
Some

Disease.

Healthy volunteer

③ > 18

④ _____

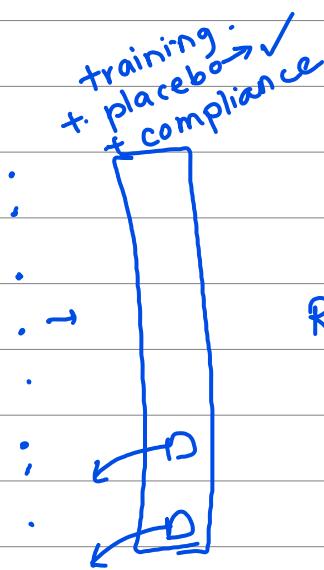
⑤ _____

Some inclusion & all exclusion criteria
follow
not followed

Run-in Period

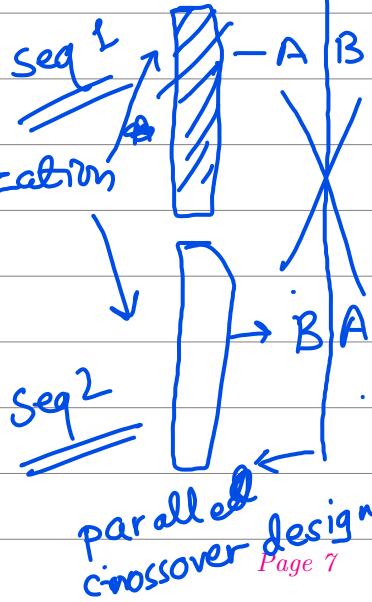
inclusion &
exclusion
criteria

Titration
design



+ training
+ placebo
+ compliance

Randomization



parallel
crossover design

?

Titration design - ①

②

③

④

⑤

⑥

Upward

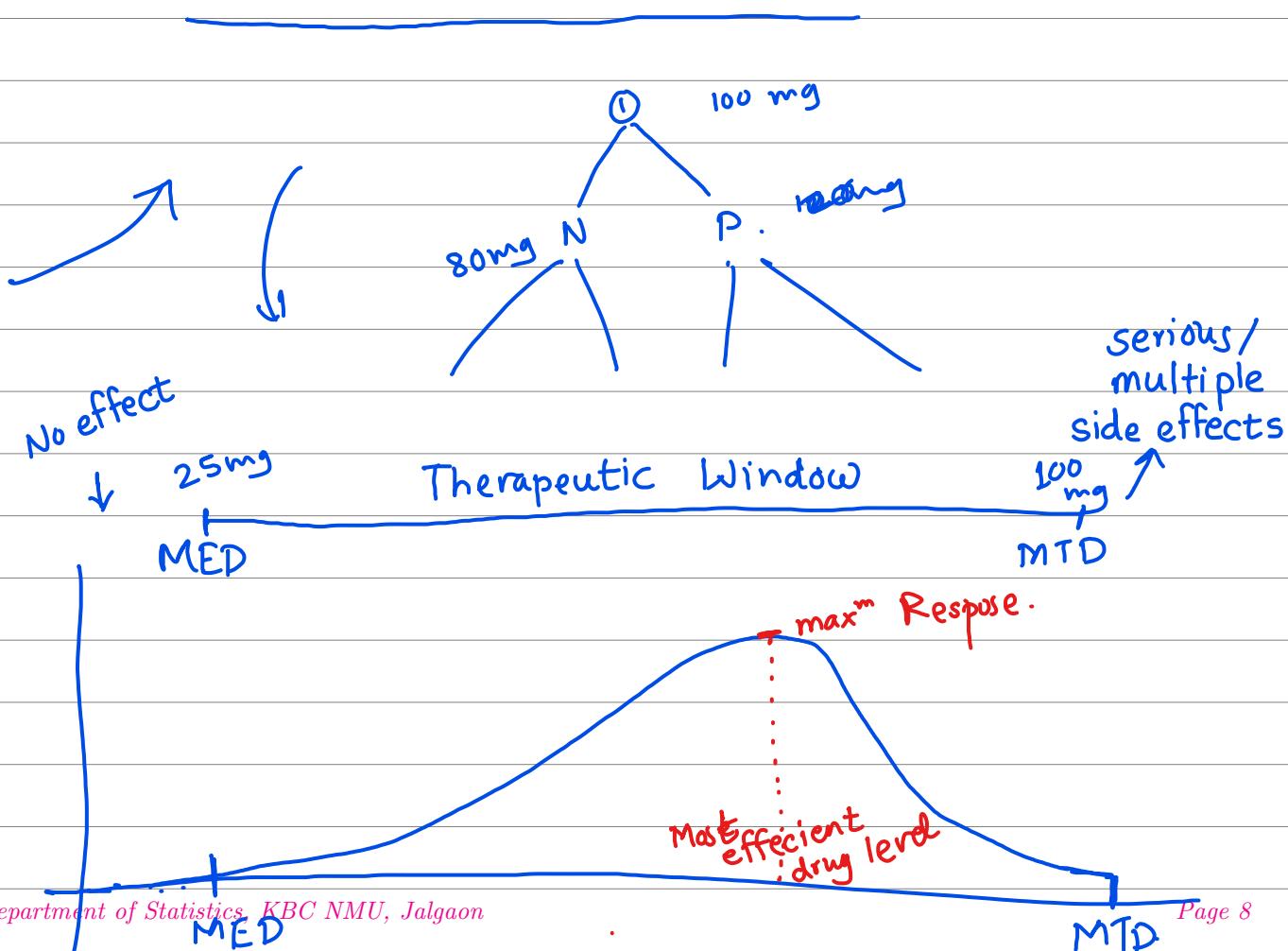
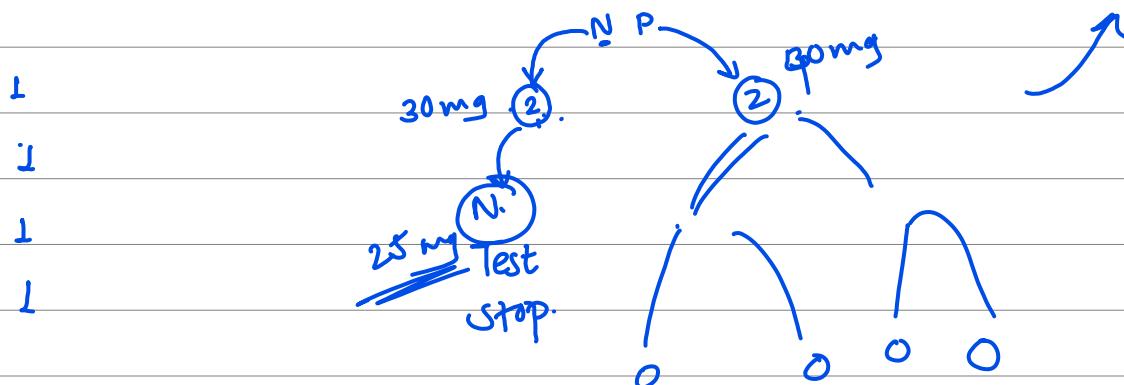
Upward-downward

downward

Human

Safety

① . 30mg -



① Methods of blinding

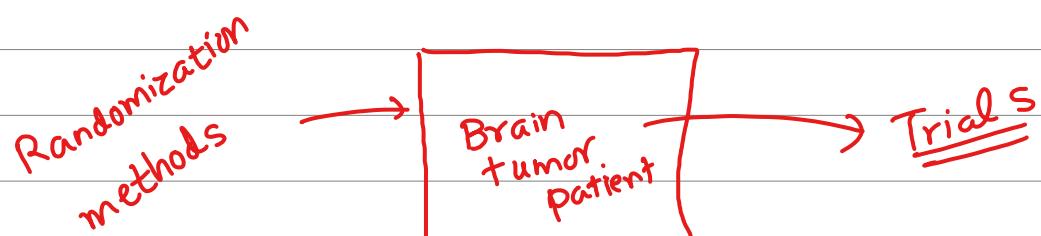
- open label** ① No - Everyone knows
- ② Single - Patient / Dr. any one is blinded
- ③ Double - & no one knows the allocations
- ④ Triple - Patient / Dr / Other staff all are blinded
↳ Data collectors - Nurse

Data Analysts - Statisticians

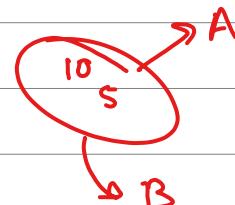
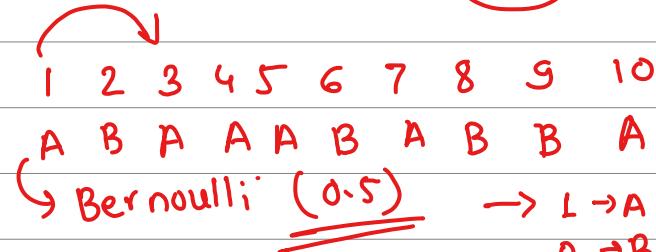
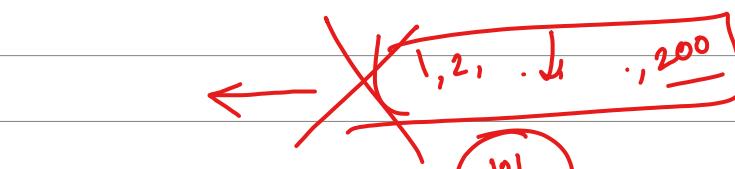


* Randomization ✓

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

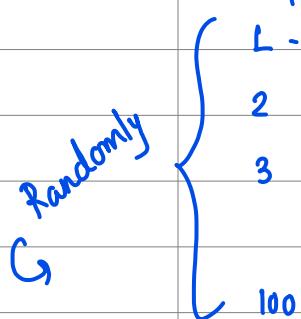


Randomization
Assignment of patients to treatment groups



① Complete Randomization

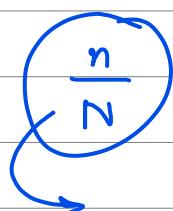
drugs
A & B assign with equal prob.



using R → SRSWR
① sample

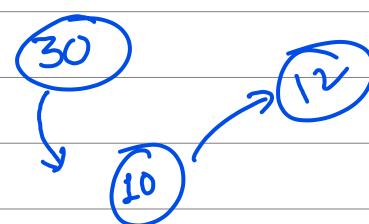
② Bernoulli: — $0.5 \rightarrow L \rightarrow A$
 $0 \rightarrow B$

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?

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

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

Randomization

① Patient Popn → ^{Random} Sample drawn

Invoiced popn

② Patient - Drug assignment

100,000
100 → Treatment

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 ✓

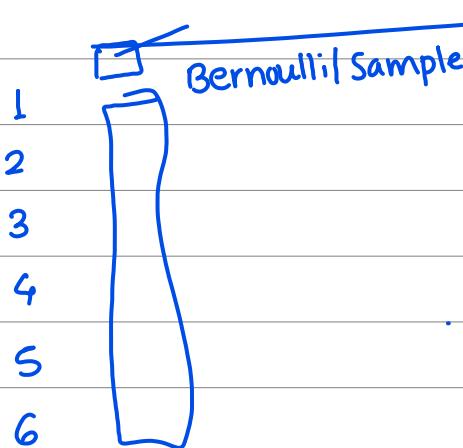
A 1 4 6 ✓ $n(A) = 3$

B 2 3 5 ✓ $n(B) = 3$

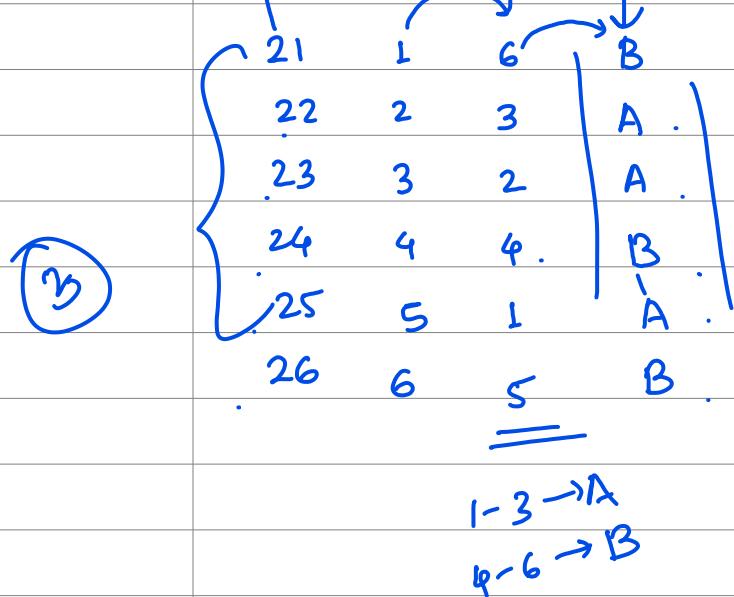
$(1 \ 2 \ 3 \ 4 \ 5 \ 6) \rightarrow$ Random Sample without replace
A A A

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	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

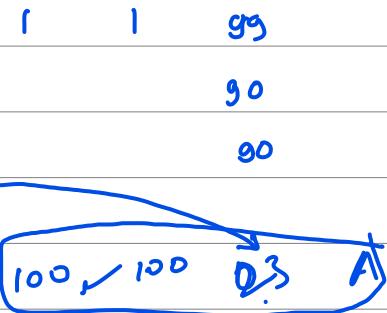
30 patients divided into 3 blocks

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

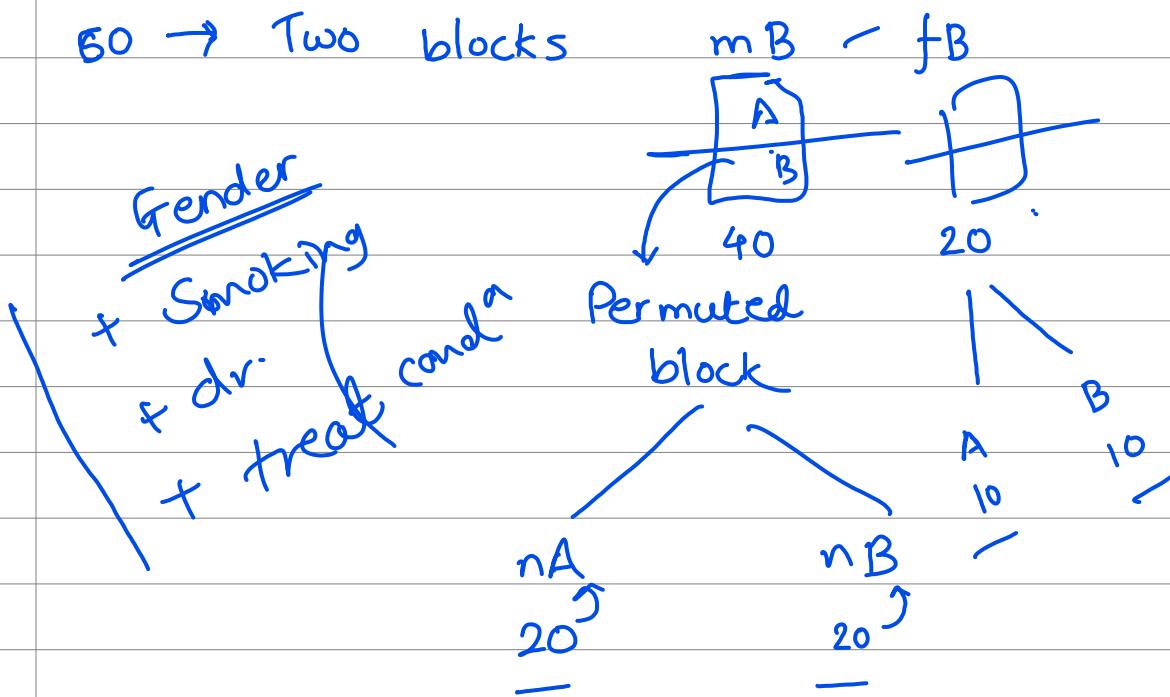
Adaptive Randomizations

① Treatment Adaptive Randomization

② Covariate A R

(Stratified Randomization)

③ Response A R



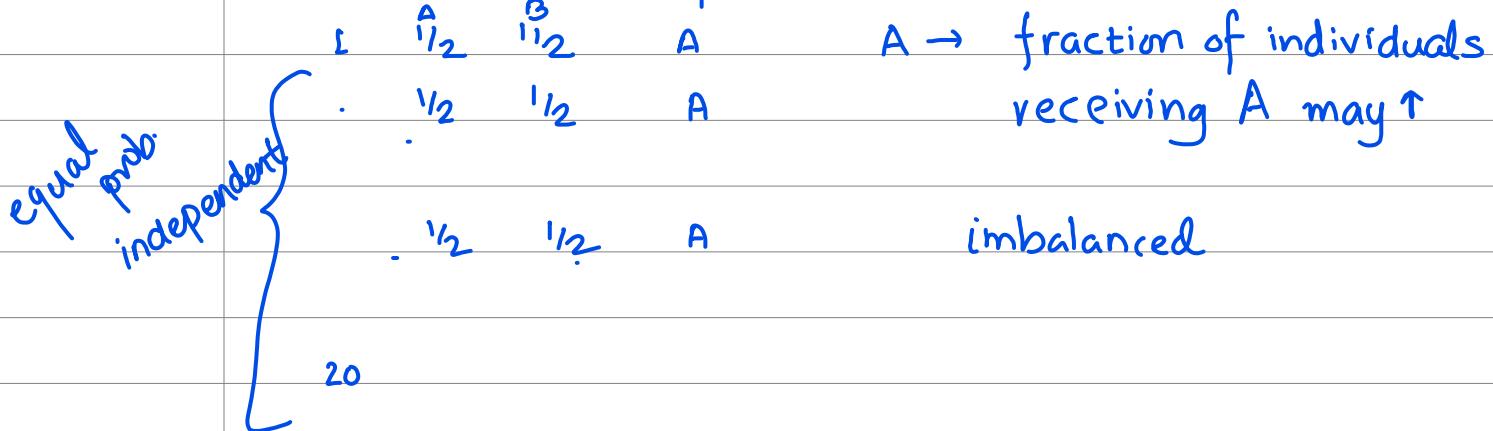
* Covariate :- Strata \rightarrow Covariate - Seq's -

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

Covariate - Groups - ✓ Permutated

Complete - Randomiz. 4 - NM

* Treatment Adaptive Randomization



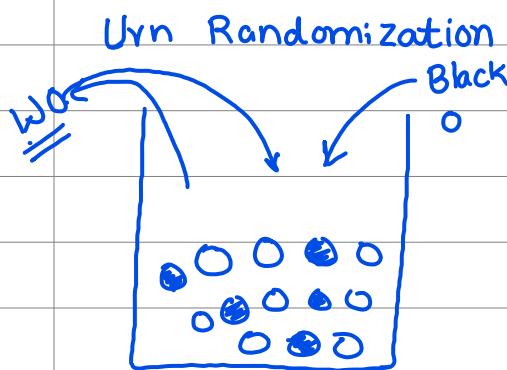
Efron (1971)

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

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

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')

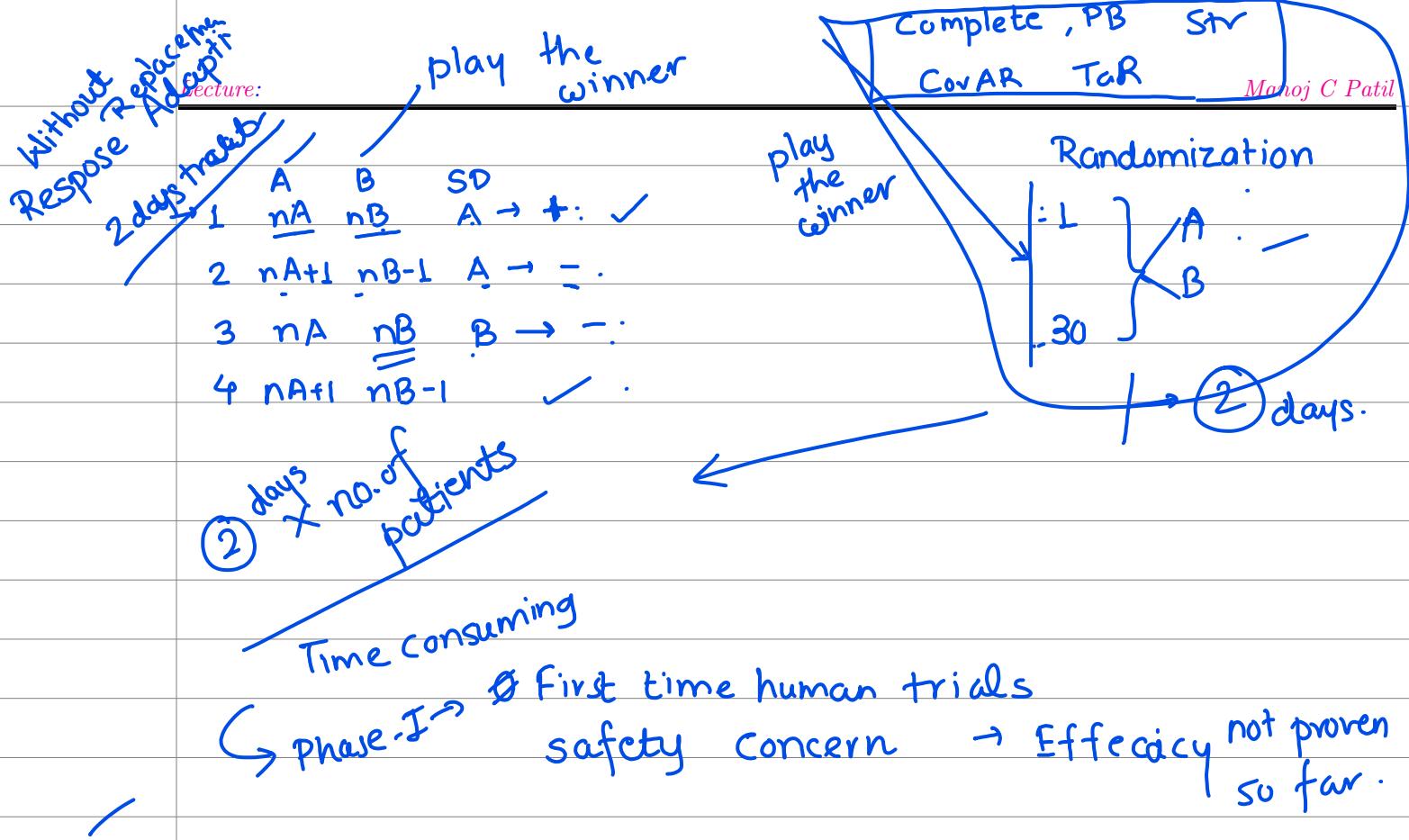
tre[1] =

✓ 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
}
  
```

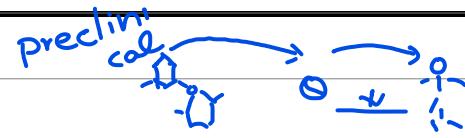
* Response Adaptive Randomization
(Play the winner -)



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

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

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^{4 part}

- Dose Range

extended phase II trials - Effectiveness

Physicians Label

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

⇒ Drug Approval Process

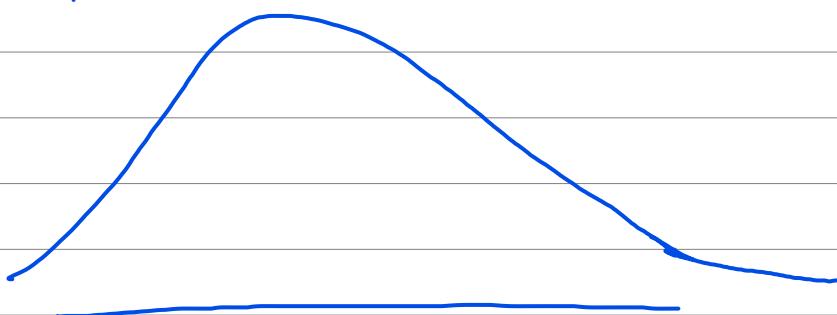
Trials → Phase IIIIB

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

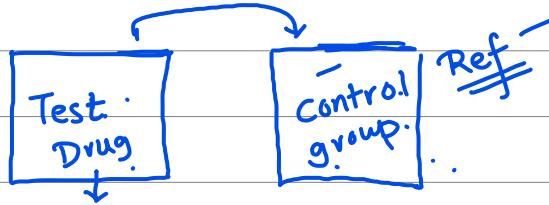
Ref: ① No treatment

② Placebo treatment

✓ ③ Active Drug

④ Dose-response concurrent

⑤ Historical concurrent



Drug is effective

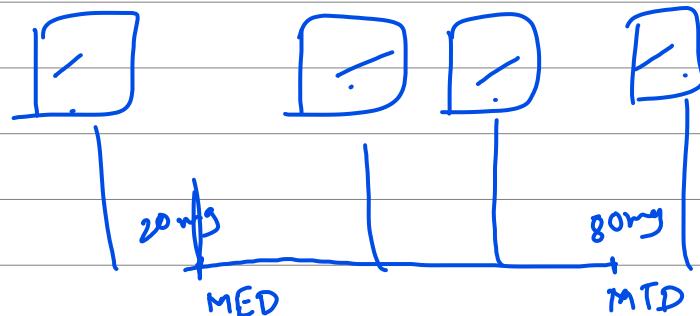
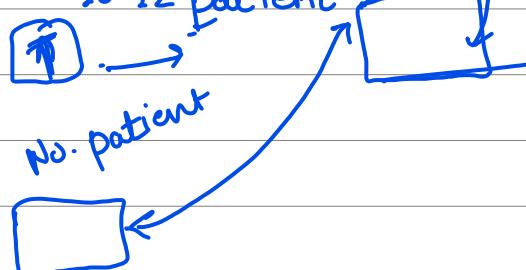
(Therapeutic window) concurrent control

↑
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 \approx 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

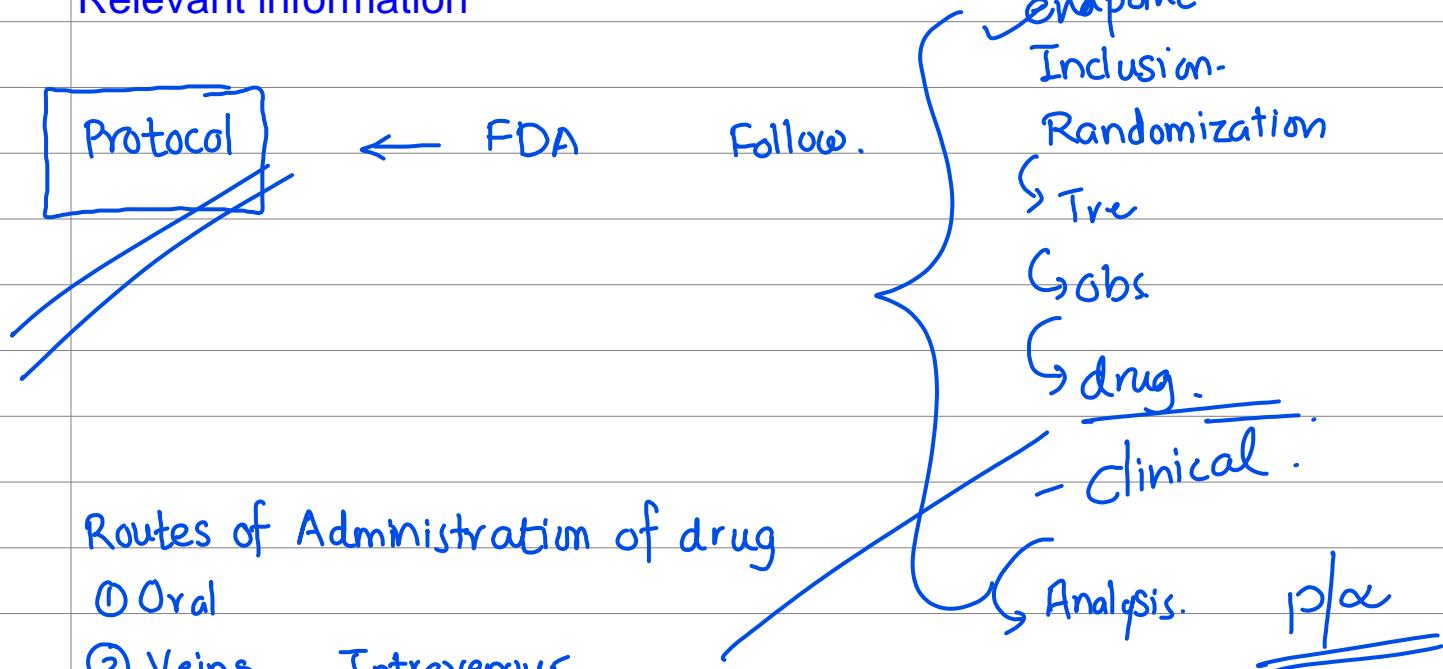
→ Govt Health dept

→ 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



Center 14 Test 01 Sub 001

1401001
1502009
= = =

Labelling

- potential bias

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

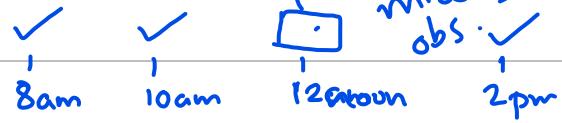
Ref

+ Milk ✓
 + Drug B ✓

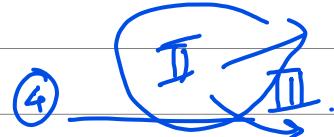
① Dropouts ? Treatment →

who fails to complete

② missing value



1 → g_{max} ③ Premature Termination.
 ② 7 pre

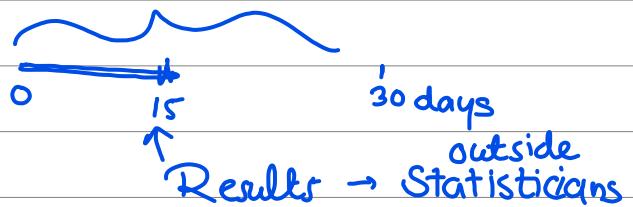


* Multicenter Trials :- ?

① No. of pat subjects ↑

② Results generalizable

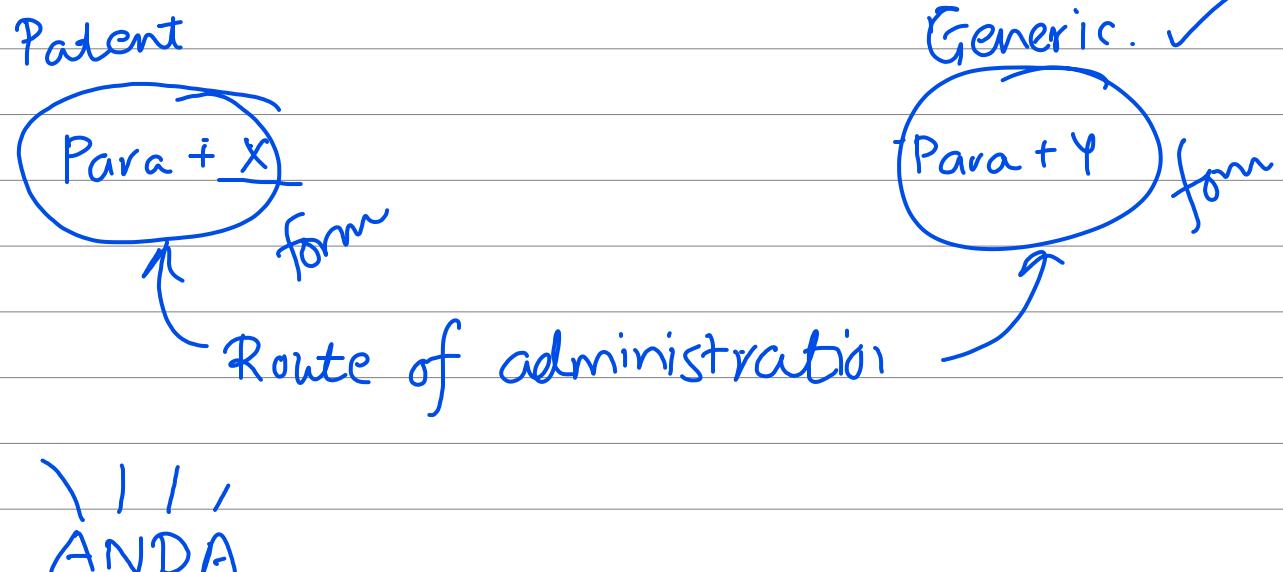
* Interim Analysis



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

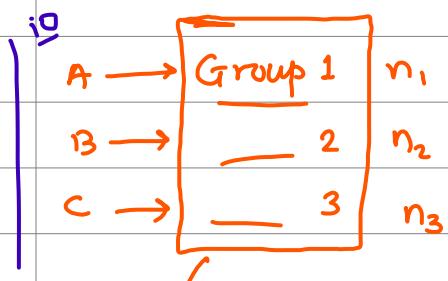
A.	<u>1,4</u>	2
B.	2,5,8	3
C	3,6,7	3

Replication

① One-way

A B C

$\mu_A = \mu_B = \mu_C$

homogenous
Group formation?Comparable
Uniform

↳ Randomization? Unbiased

↳ Reduce-bias & variability

Anova :- F dist

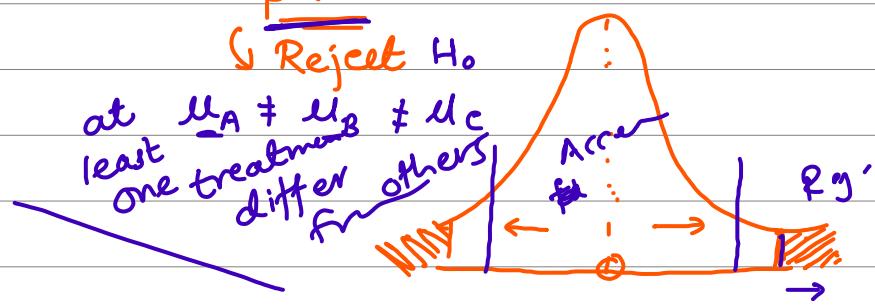
 F_{crit-2} $F_c < F_{table}$

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

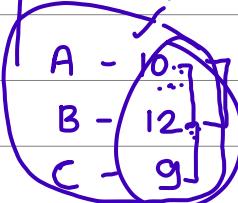
$$t = \frac{(\bar{x}_A - \bar{x}_B)}{\sqrt{MSE \left(\frac{1}{n_1} + \frac{1}{n_2} \right)}}$$

Two-Sample t test

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

Pooled

$$\hat{\sigma}_p^2 = \frac{(n_1-1)\sigma_1^2 + (n_2-1)\sigma_2^2}{n_1+n_2-2}$$



② Two-way

Two factors - different levels

① Smoking habits

②

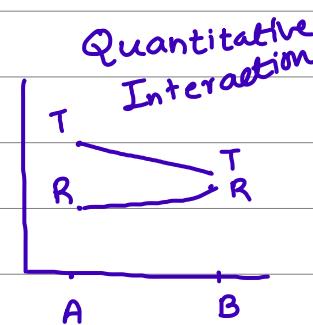
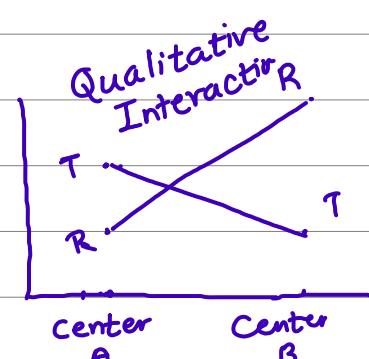
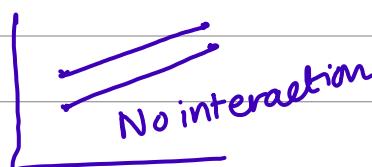
	Smoker	Non smoker
low	n_1	n_2
Moderate		
high		



r fobs per cell

③ General two way

Interaction Effect

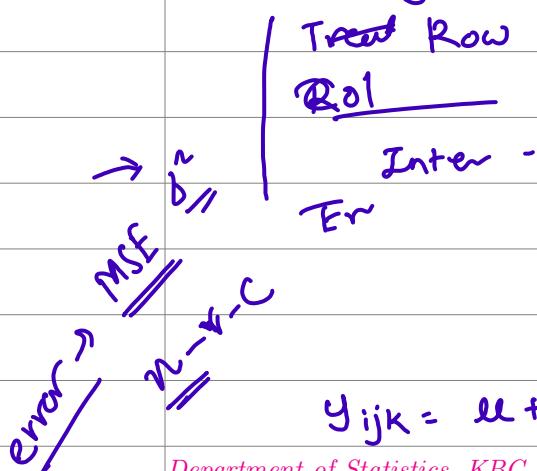


④ Factorial Designs? -

2^k factorial
↑ No of factors
levels.

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

Two-way with inter



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

sign

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

Interaction

effect identify

Confounding ?

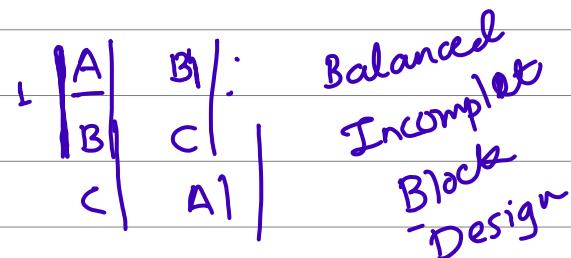
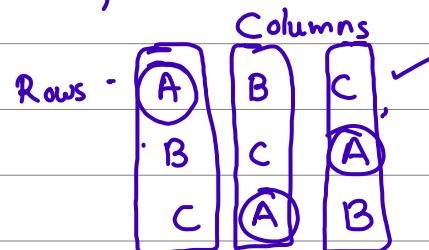
- due to some identified/unidentified factor effect

CRD RBD
1 2 3 Factorial

LSD

Latin Square Design

3 factors



Designs CT

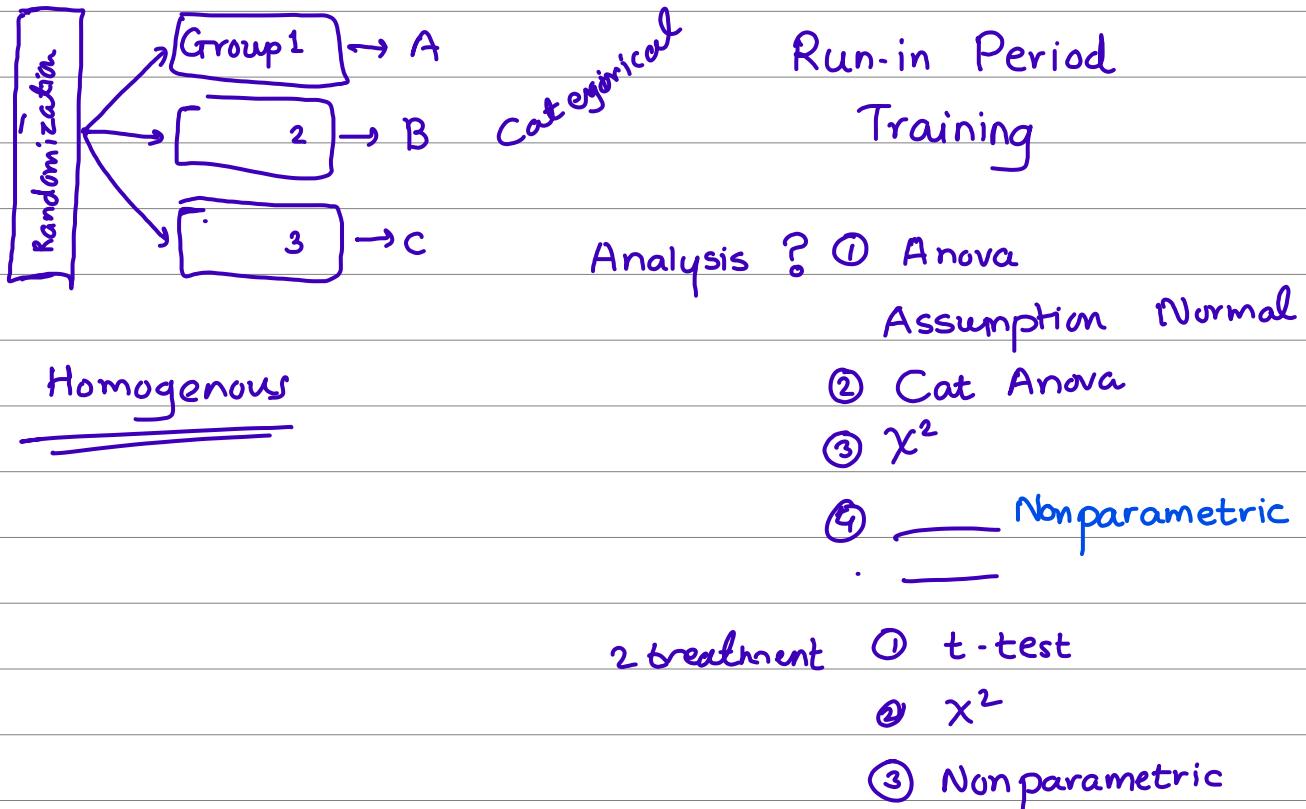
Obs: ① Test treat > better
Refere

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

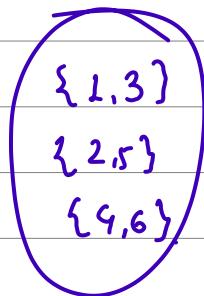
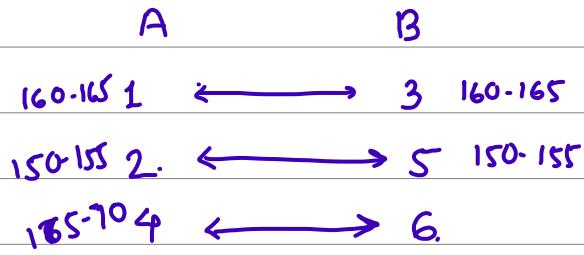
Control :-

Active Concurrent Controls

* Parallel Group Design 3 treatment A, B, C



Matched Pair



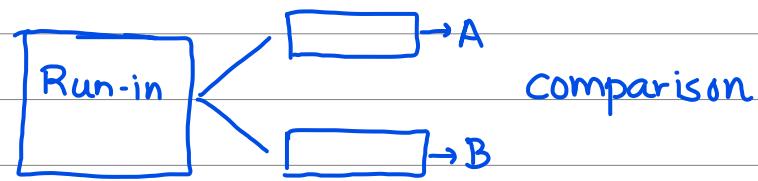
Abs : 4, 6, 9, 10, 13-14, 16, 22, . 30, 33-35, 39, 43-47, 50, 51, 53-55 = Total present 37

Variability \rightarrow Intersubject - Between - Patients
Intra subject - Within - Patient

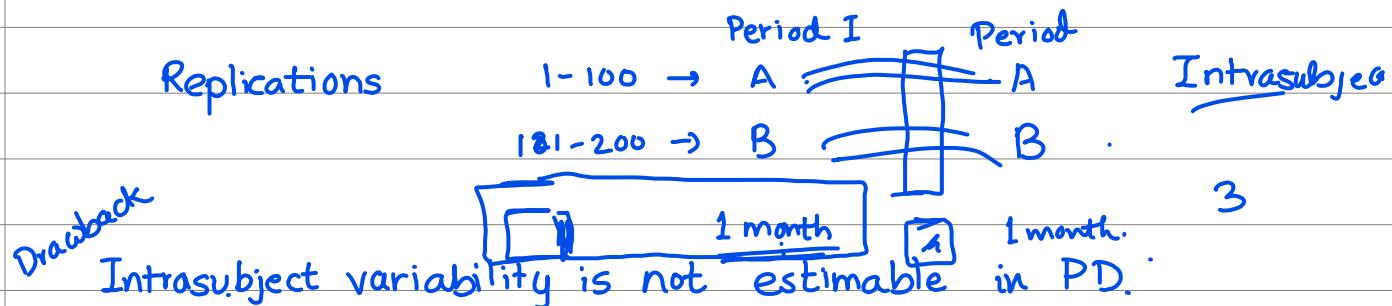
Variability \rightarrow Intersubject :- Same Single treatment \rightarrow diff sub \rightarrow diff responses variation.

Intra subject :- Same treatment \rightarrow same patient - diff time points within patient

Parallel Design



$1-100 \rightarrow n_A$ patients - Drug A estimator $\mu_A \delta_A \leftarrow$ Intersubject ✓
 $101-200 \rightarrow n_B$ - Drug B $\mu_B \delta_B \leftarrow \dots$



Run-in Period

Recruitment ↗ A ↗ B

① Training ✓

Sc

7-730 → 8 = blood n

Drug A → hour ↘ Low / Mod / High ↗

② FIR - baseline variable

↳ Covariate ↳

↳ Inclusion Exclusion Criteria

LOG F

gg F

baseline ✓

Clinical endpoint

③ Placebo respondent identify

④ Patient compliance

Nil by mouth

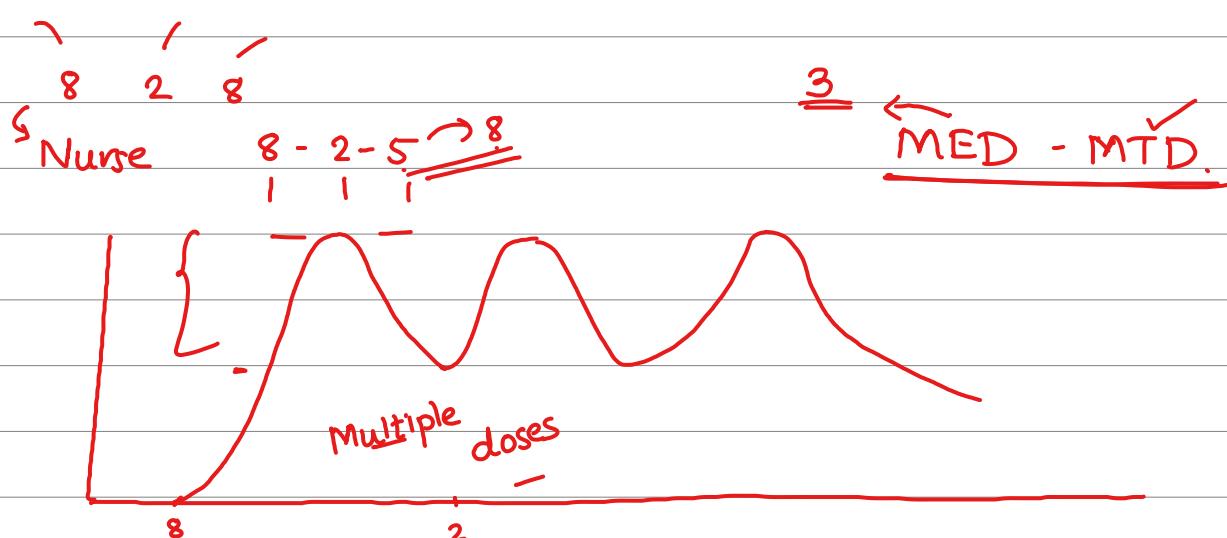
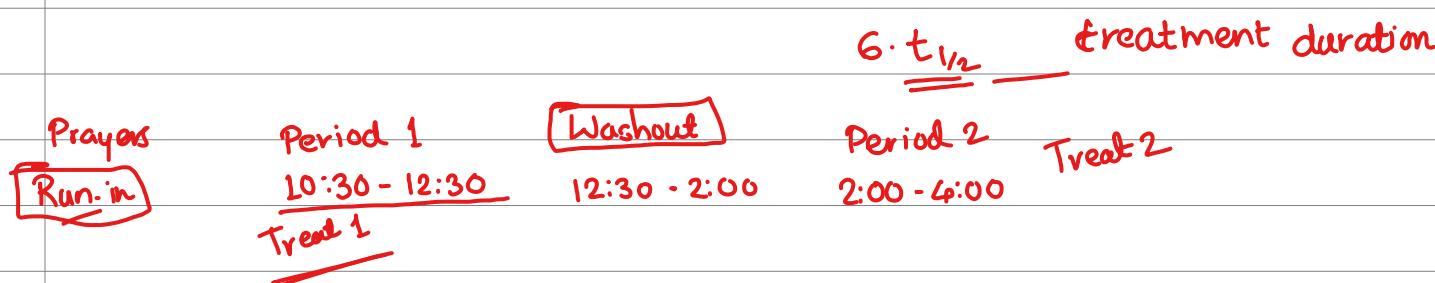
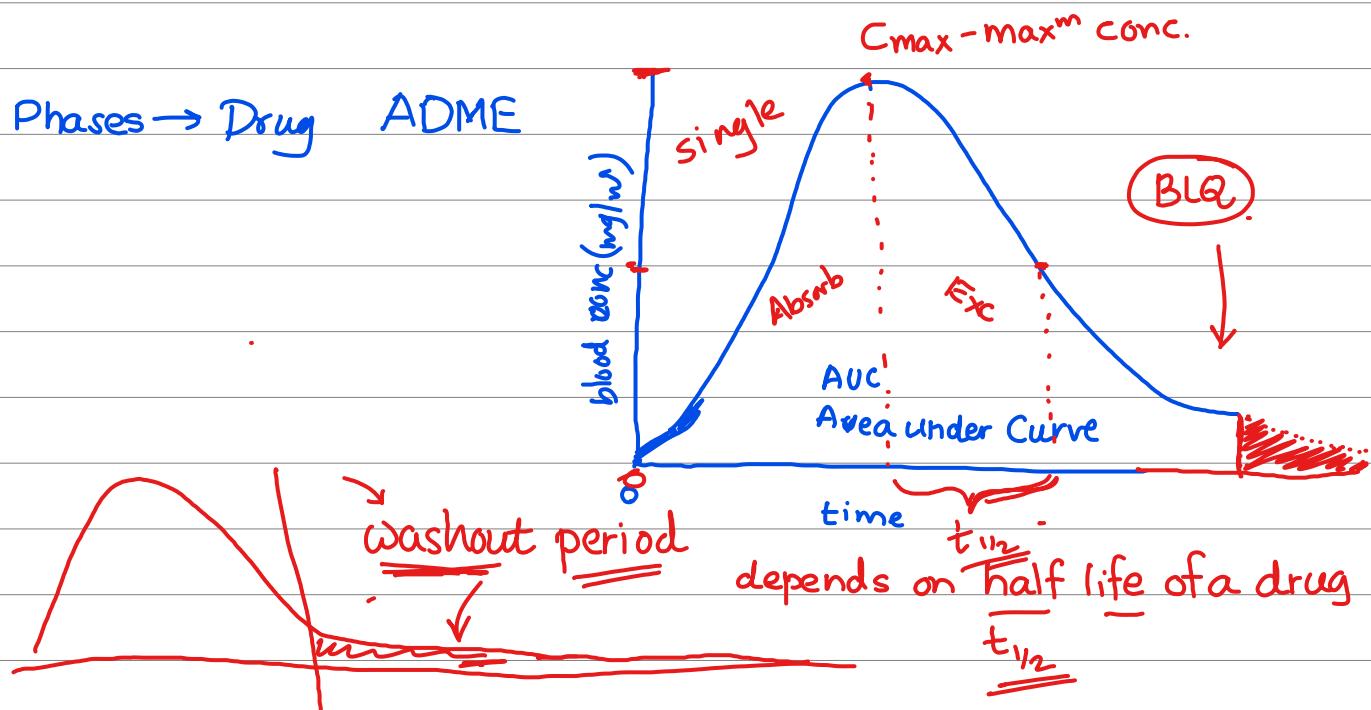
⑤ Washout period

for previous treat



② 8 10 12 2 4
 | | | | |

8 10 12 2



Treatment Effect

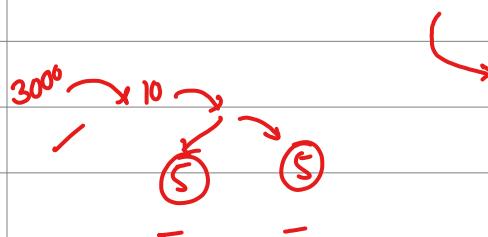
① Active ingredient] X I

② Placebo

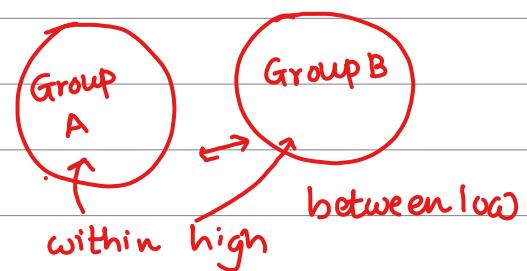
③ Disease] ✓

④ Other factor] ✓

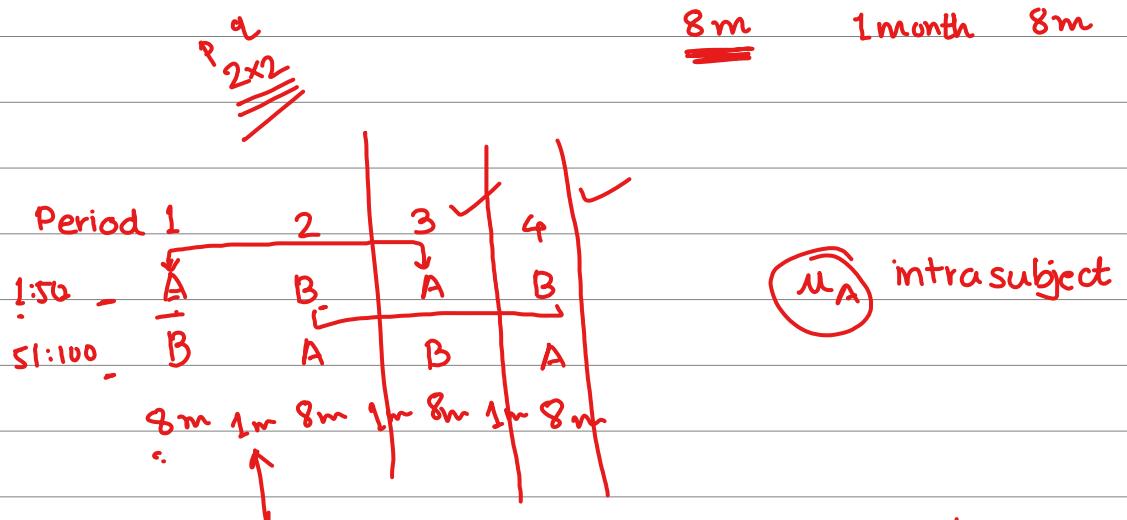
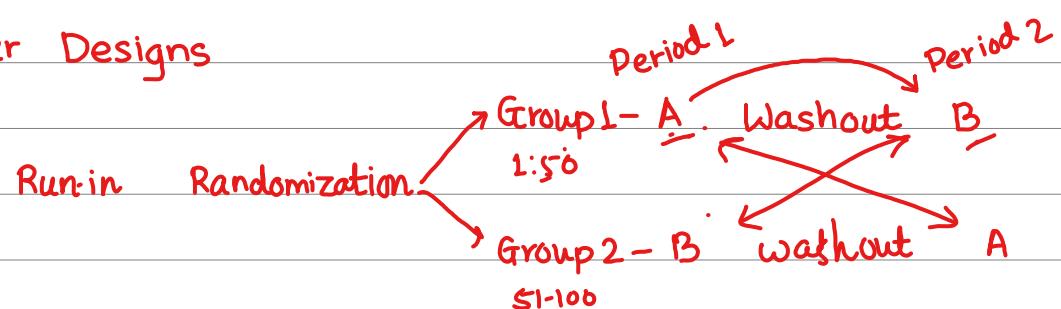
✓ Cluster Randomized design



ST-103
Cluster Sampling ?



Cross-over Designs

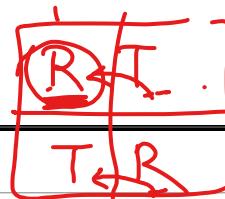


Complete Crossover

1 → A B B B
2 → B A B A

1	2
1	A B
2	B C
3	C A

$\frac{P \times q}{3 \times 2}$
say period



$$Y_{ijk} = \mu + F_{(j,k)} + P_j + S_{ik} + C_{(j-1,k)} + \epsilon_{ijk}$$

general mean effect

subject period seqⁿ

washout period = Random

		Summer	Winter	
		Period 1, j=1	Period 2 j=2	
Seq 1 \Rightarrow	$K=1$	$E(Y_{11}) = \mu + F_R + P_1$	$E(Y_{21}) = \mu + F_T + C_R + P_2$	$1: w_1$ n_K
	$K=2$	$E(Y_{12}) = \mu + F_T + P_1$	$E(Y_{22}) = \mu + F_R + C_T + P_2$	$1:n_2$

2x2 //

Random Effect Models

$$Y_{ij} = \mu + \alpha_i + \epsilon_{ij}$$

fixed Random

Fixed effect Models

$$Y_{ij} = \mu + \alpha_i + \epsilon_{ij}$$

fixed Random

$S_{ik} \sim N(0, \sigma_s^2)$
i.i.d.

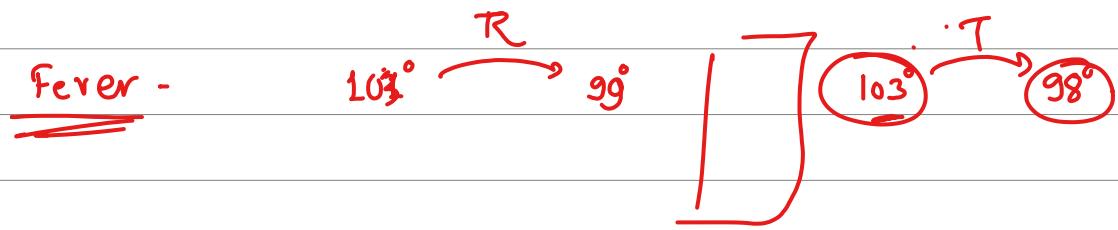
S_{ik}, ϵ_{ik} indep.

$\epsilon_{ik} \sim N(0, \sigma_e^2)$
i.i.d.

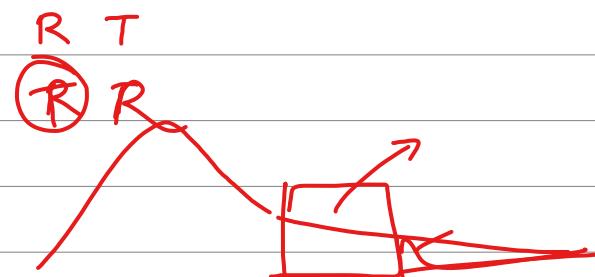
~~C_R - C_T~~ $C_T - C_R$ = Carryover effect

Cross-over design

period seqⁿ
p x q



Interview, Case Study



Absent:

2003, 6, 9, 10, 15-17, 25, 30, 35, 39, 43-47, 51, . = 38

