

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

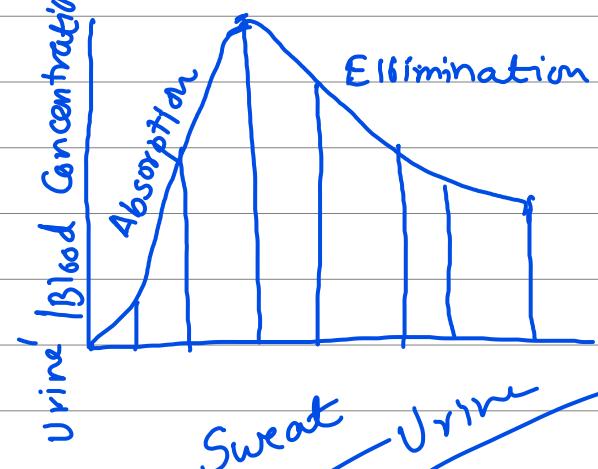
Pharmacology

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

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

Phase-I

\rightarrow 20/80 \rightarrow side effects min

II

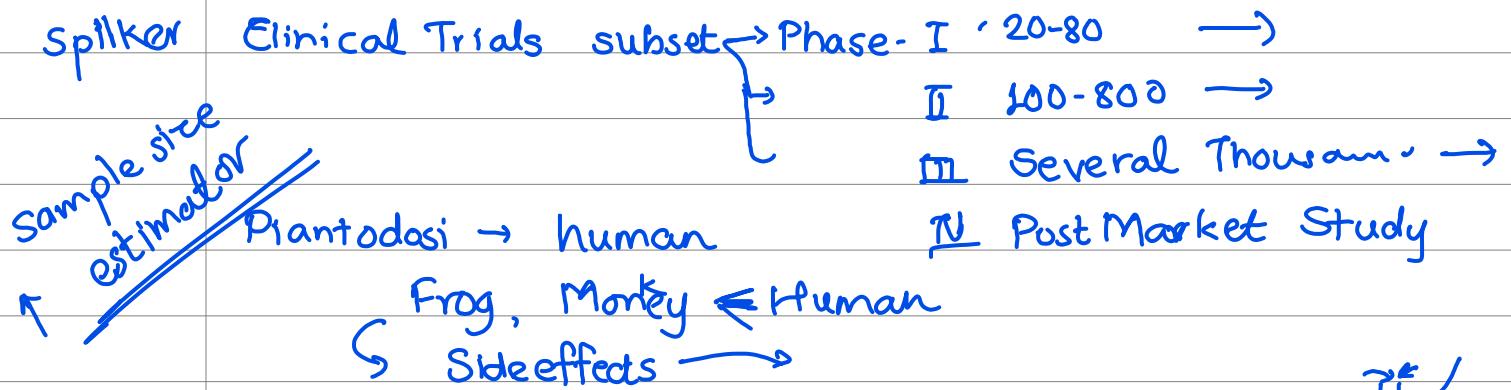
\rightarrow 800 - 1000 \rightarrow effectiveness side effect

III

\rightarrow Thousands \rightarrow Physicians labelling

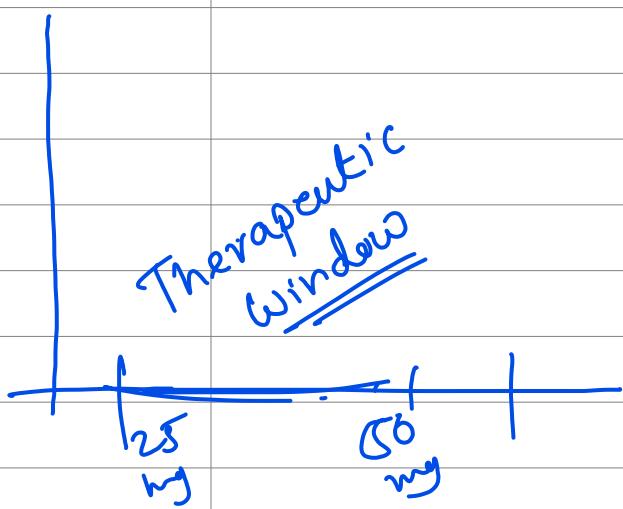
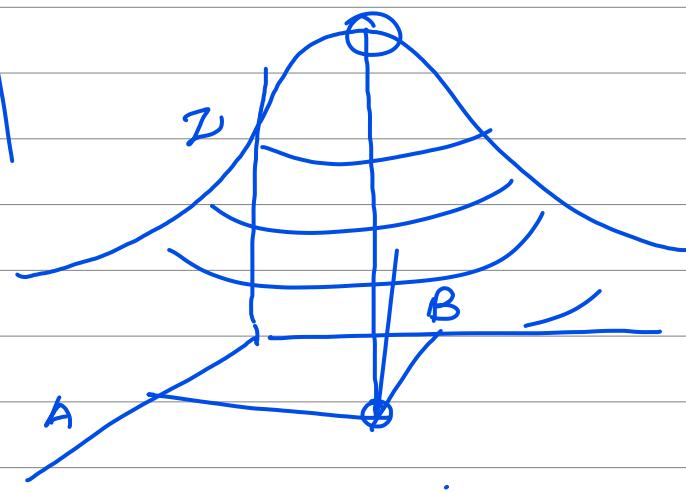
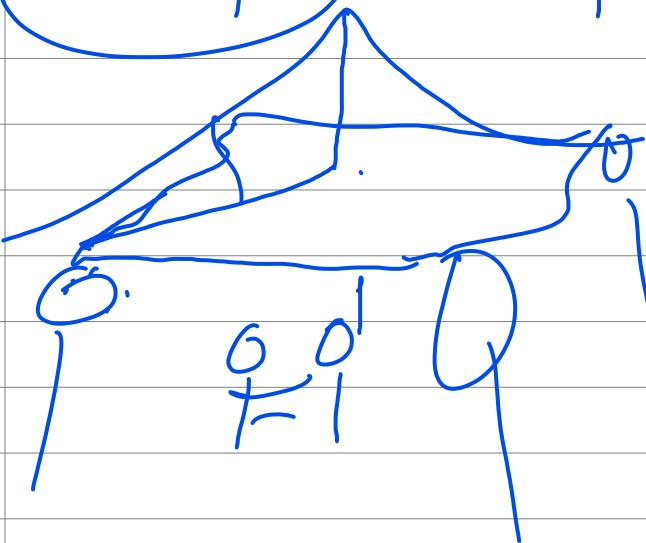
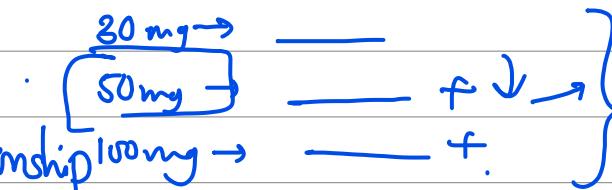
IV

\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

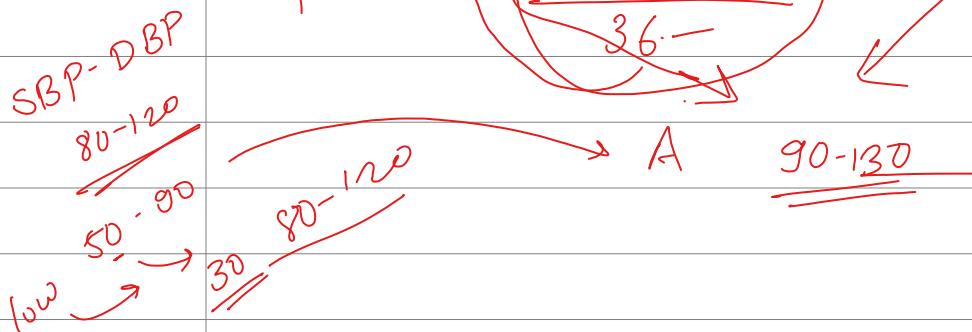
36 -

Clinical diff

LSL ?

USL ?

Clinician / Doctors



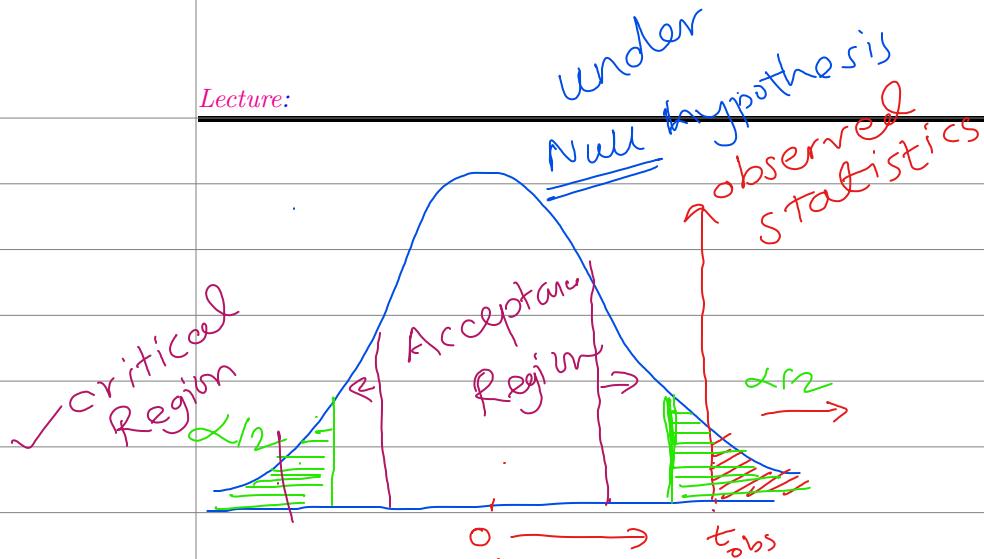
$$\beta = \mu_B = 110$$

$$\delta_B = 2$$

$$98 - 122$$

some

Clinician



$$\alpha > p$$

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

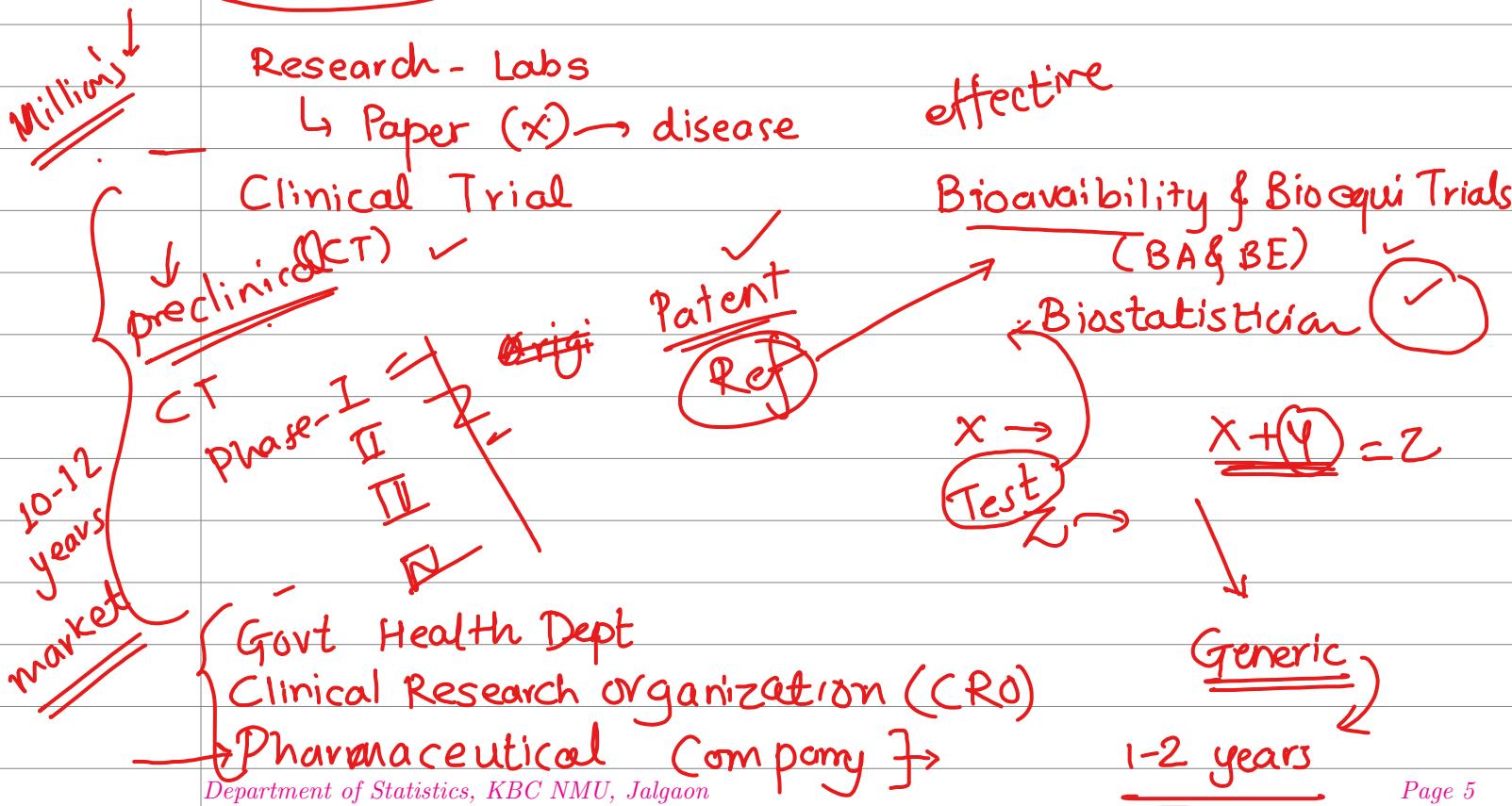
$p > \alpha \Rightarrow \text{fail to}$

$\text{Reject } H_0$

~~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

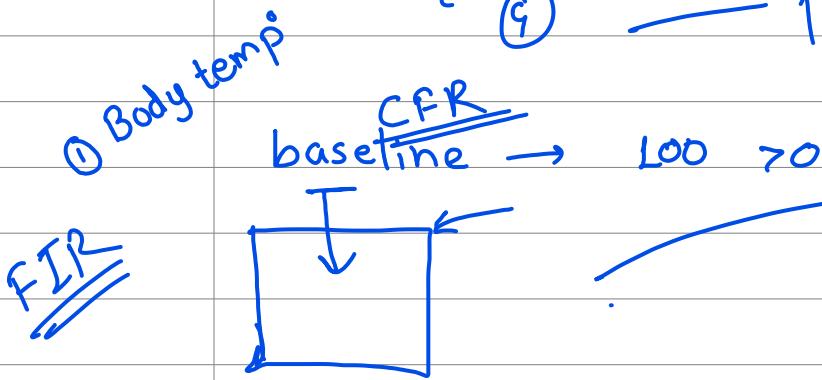
- ① Treatment to reduce weight
- ② Immunity
- ③ Muscles

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 _____

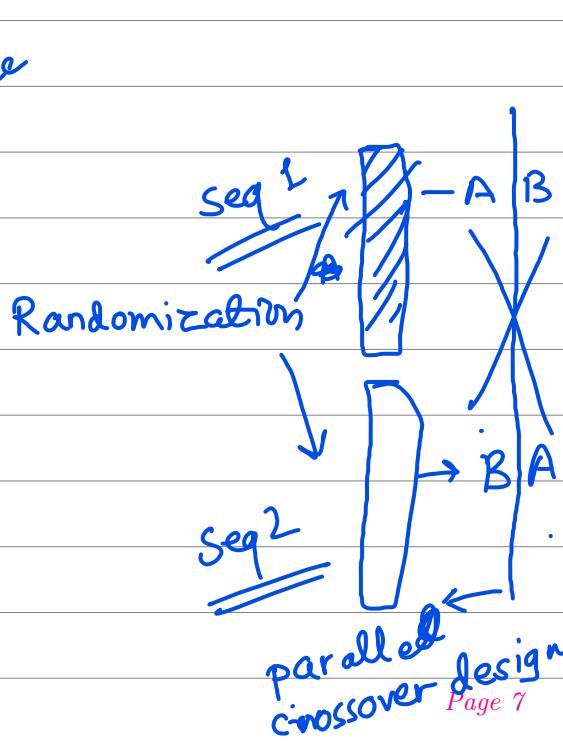
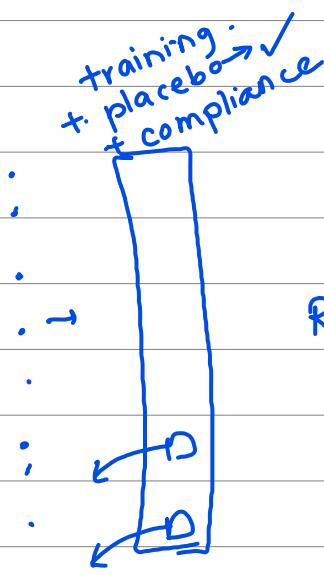
⑤ _____

Some inclusion & all exclusion criteria
follow
not followed

Run-in Period

inclusion &
exclusion
criteria

Titration
design



?

Titration design - ①

②

③

④

⑤

⑥

Upward

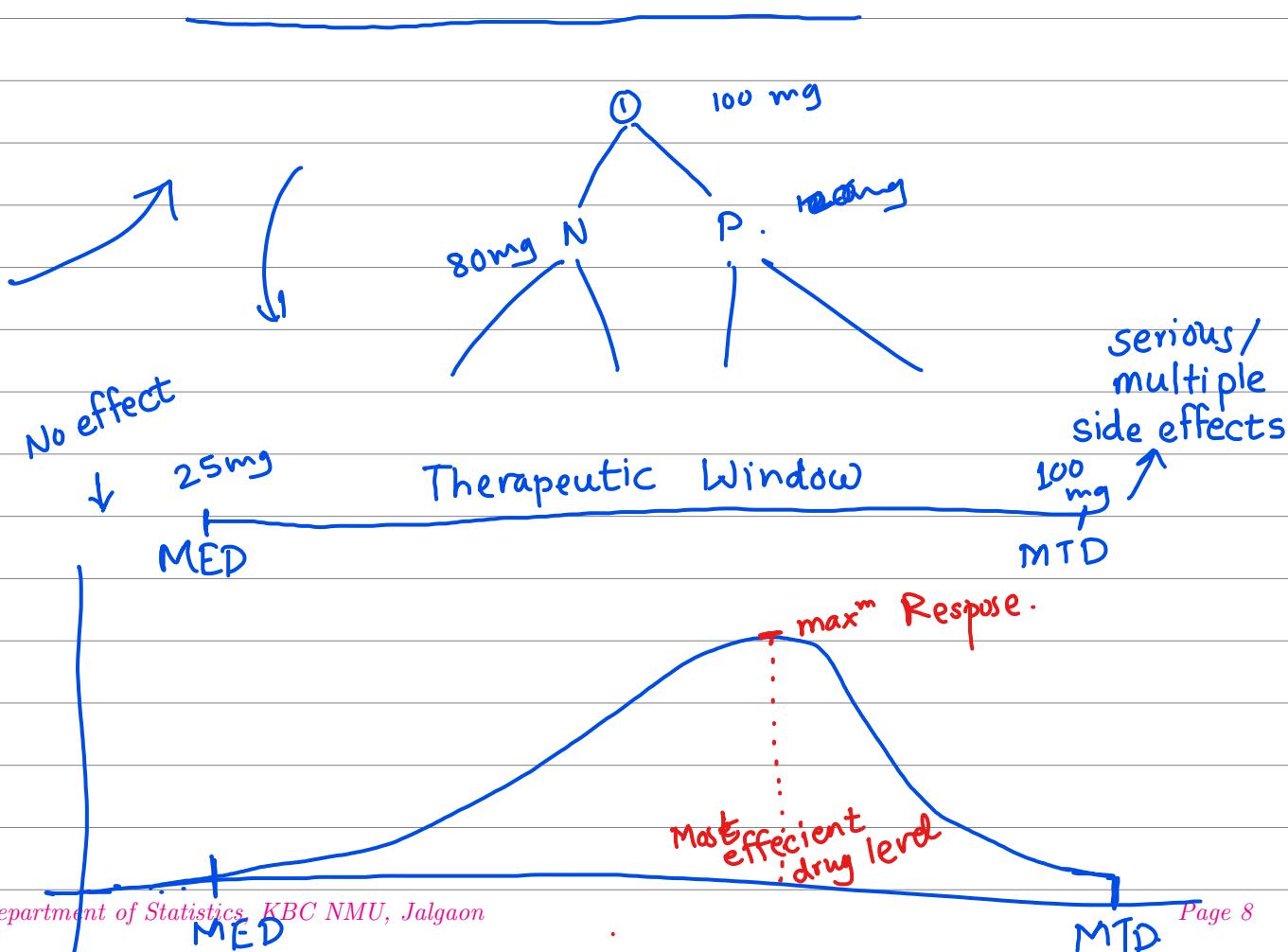
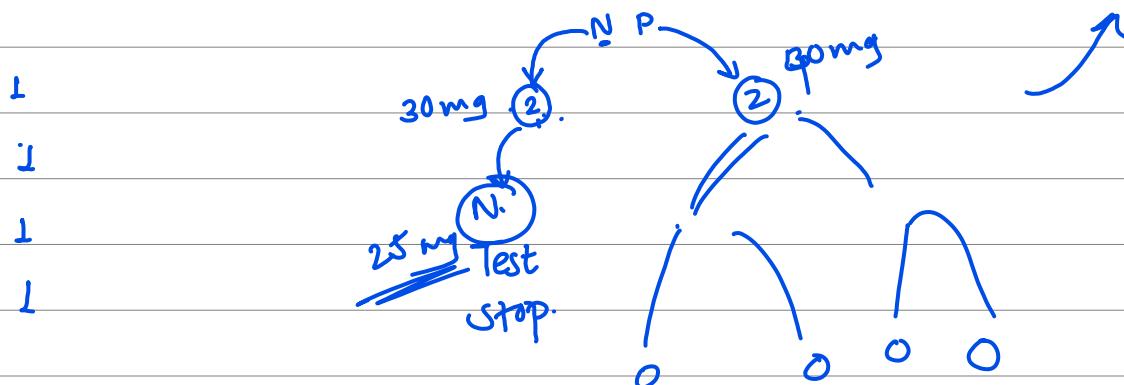
Upward-downward

downward

Human

Safety

① . 30mg -



① Methods of blinding

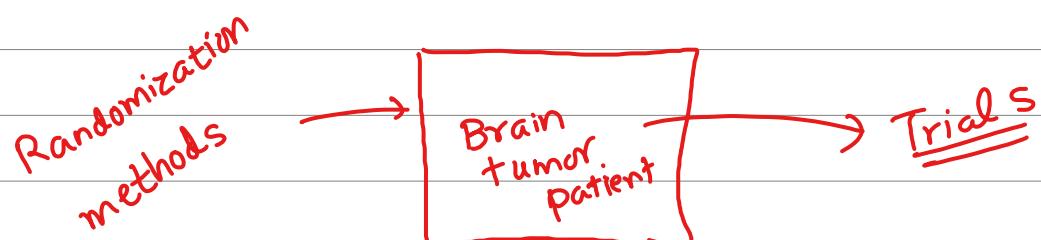
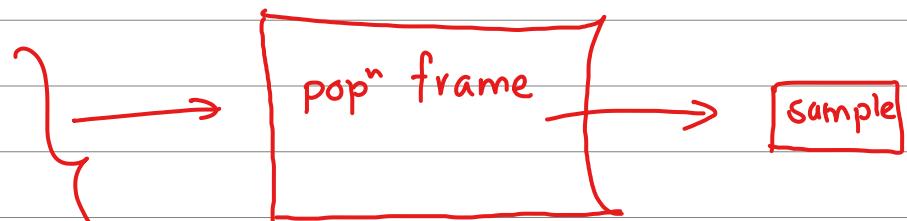
- open label** ① No - Everyone knows
- ② Single - Patient / Dr. any one is blinded
- ③ Double - & no one knows the allocations
- ④ Triple - Patient / Dr / Other staff all are blinded
↳ Data collectors - Nurse

Data Analysts - Statisticians

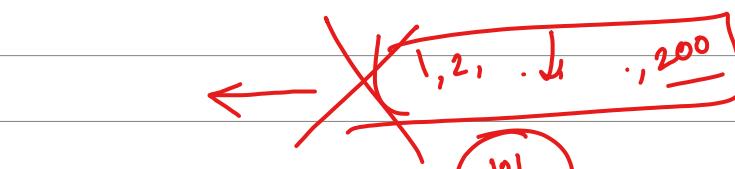


* Randomization ✓

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



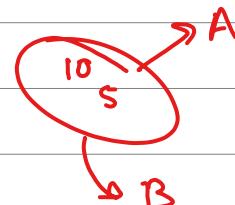
Randomization
Assignment of patients to treatment groups



Randomization
Bernoulli (0.5)

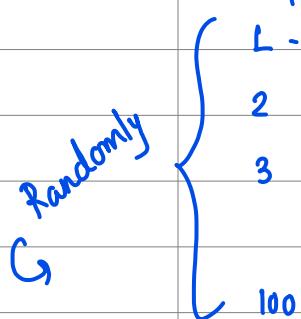
1	2	3	4	5	6	7	8	9	10
A	B	A	A	B	A	B	B	A	

→ L → A
0 → B



① Complete Randomization

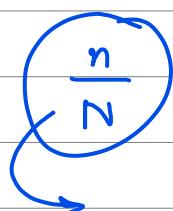
drugs
A & B assign with equal prob.



using R → SRSWR
① sample

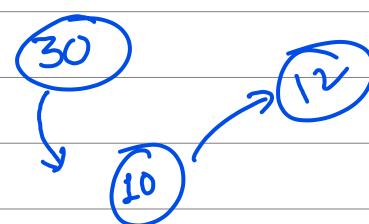
② Bernoulli: — $0.5 \rightarrow L \rightarrow A$
 $0 \rightarrow B$

③ Uniform $0.5 < 1$ A
 > B



Sample fraction

$$\frac{\min(n_A, n_{\text{placebo}})}{\text{total no. of patients}}$$



No. of individual Risk ↓

A B C Fair?

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

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

Randomization

100,000
100 → Treatment

① Patient Popn → ^{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 ✓

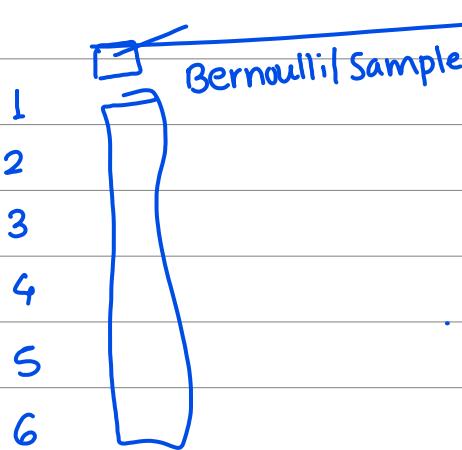
A 1 4 6 ✓ $n(A) = 3$

B 2 3 5 ✓ $n(B) = 3$

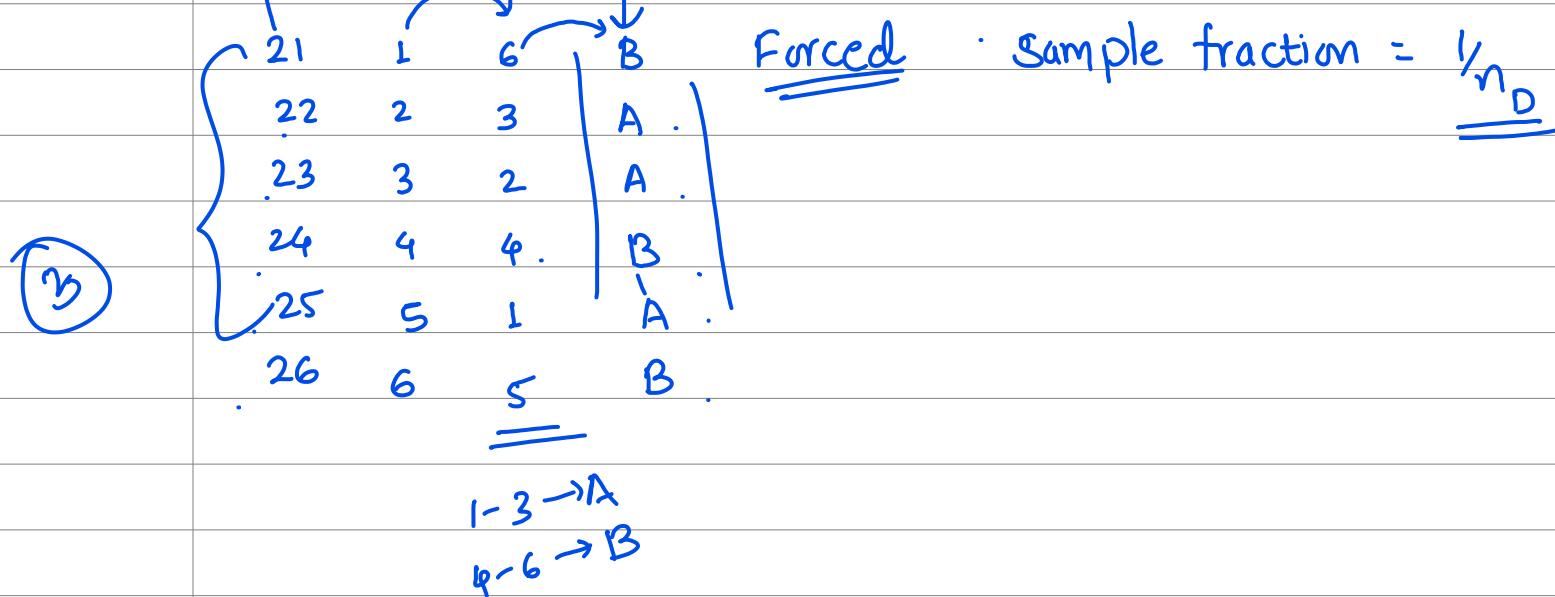
$(1 \ 2 \ 3 \ 4 \ 5 \ 6) \rightarrow$ Random Sample without replace
A A A

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	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

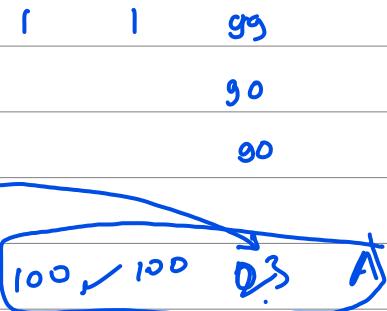
30 patients divided into 3 blocks

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

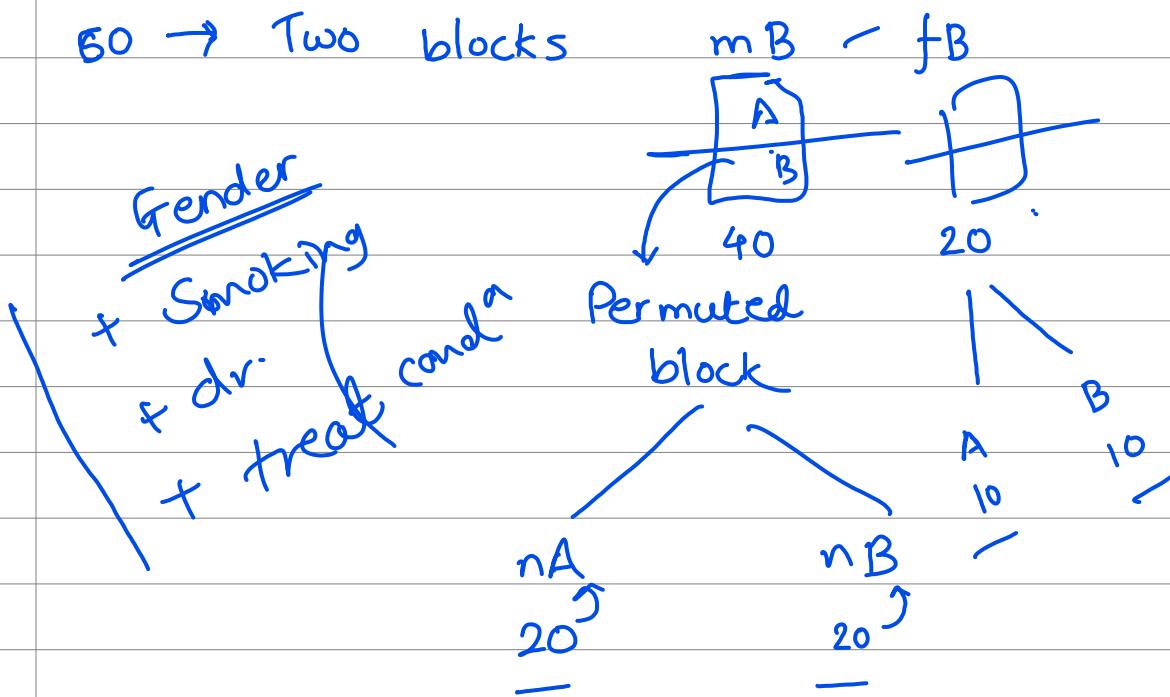
Adaptive Randomizations

① Treatment Adaptive Randomization

② Covariate A R

(Stratified Randomization)

③ Response A R



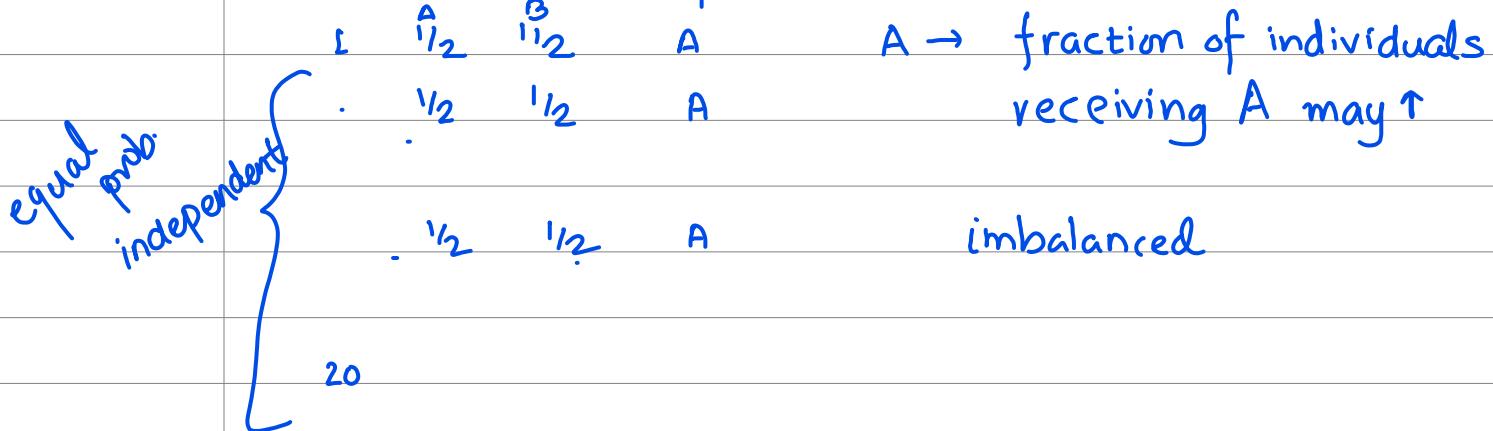
* Covariate :- Strata \rightarrow Covariate - Seq's -

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

Covariate - Groups - ✓ Permutated

Complete - Randomiz.

* Treatment Adaptive Randomization



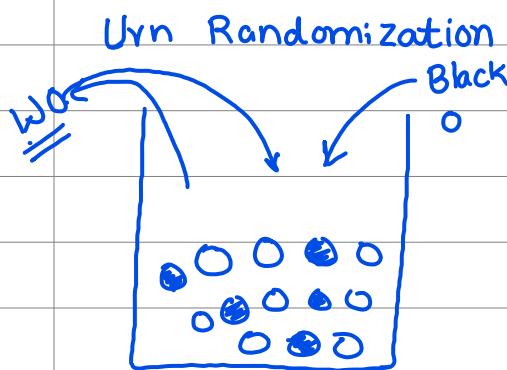
Efron (1971)

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')

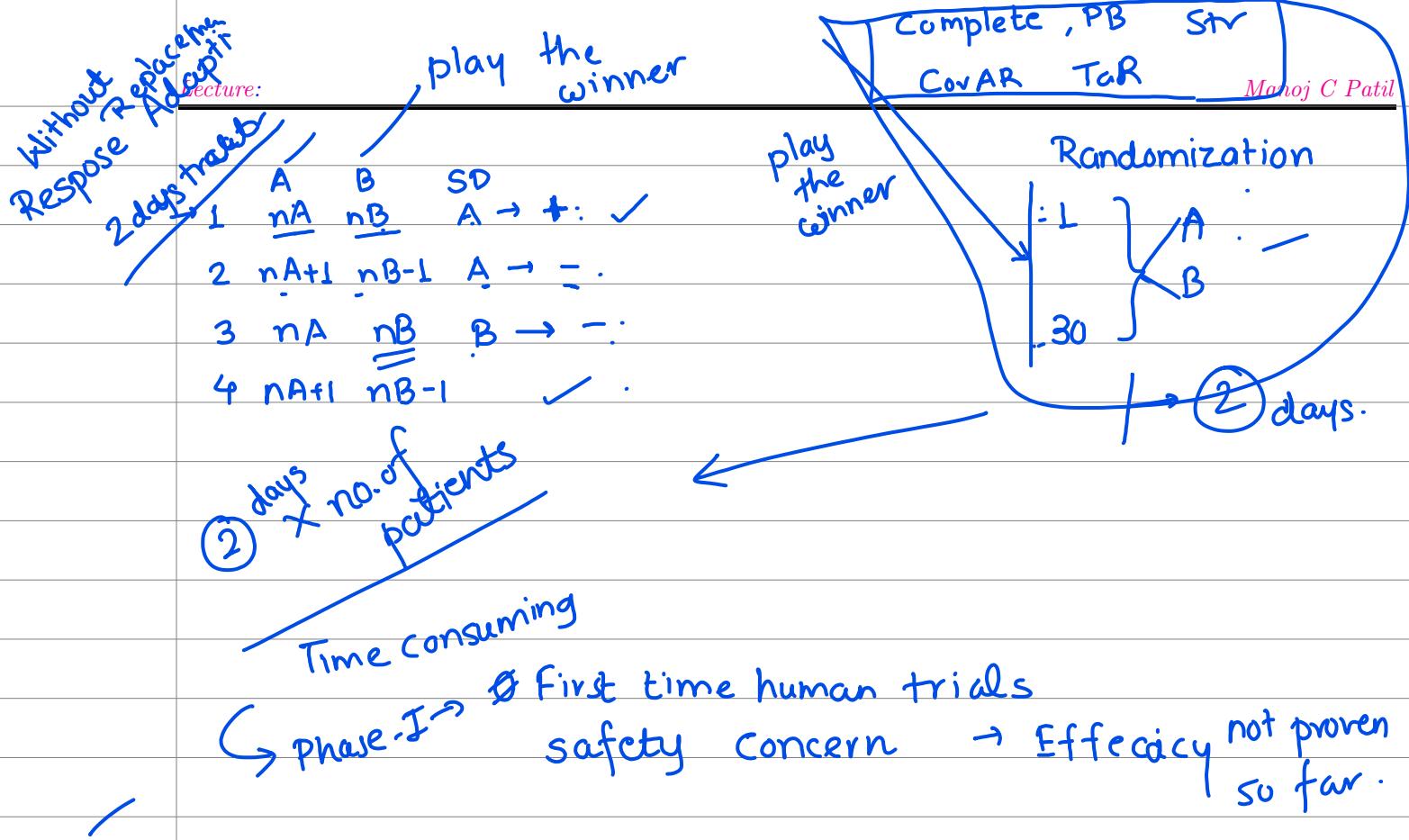
tre[1] =

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

```

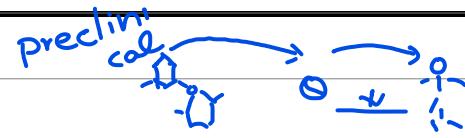
for (i=2:30){
  if(tre[i-1] == 'T') {nB=nB+1} else {nW=nW+1}
  tre[i] = Samp
}
  
```

* Response Adaptive Randomization
(Play the winner -)



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

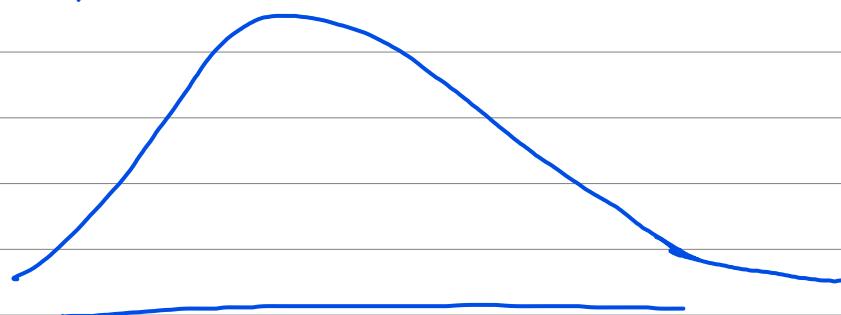
↳ Additional info effectiveness & safety needed to identify benefit-risk relationship → Drug Approval & Process Submission
Trials → Phase III B ✓

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

lower
2 side
1
same

MED Therapeutic window MTD

* Control ? ∵ Treatment

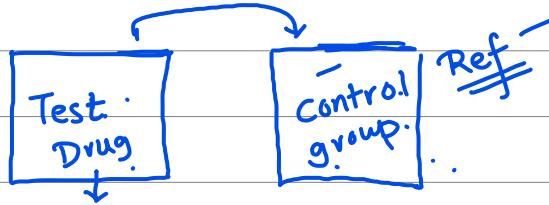
Ref: ① No treatment

② Placebo treatment

✓ ③ Active Drug

④ Dose-response concurrent

⑤ Historical concurrent



Drug is effective

(Therapeutic window) concurrent control

↑
Test

parac.

Rare disease :-

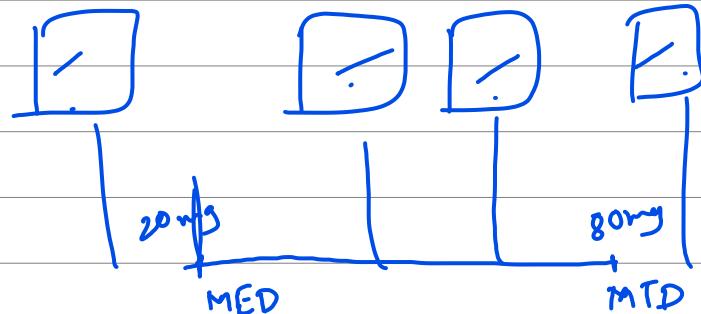
e.g. Brain tumor :-
10-12 patient



No. patient



1985
assume =



* Safety :-

Test

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

Phase-I ≈ 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

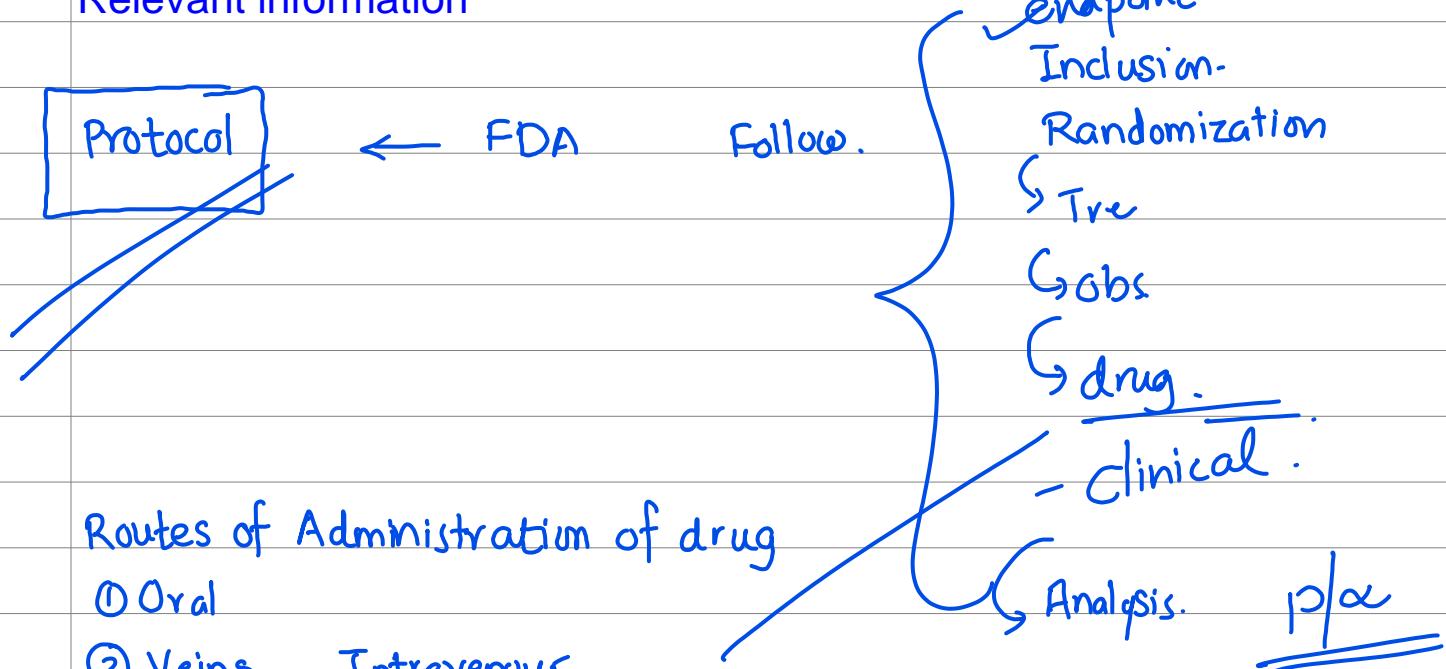
* Govt Health dept

* 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. ✓

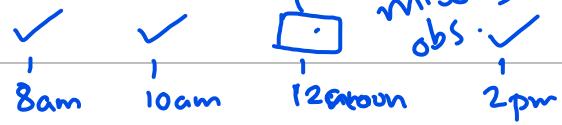
Ref

+ Milk ✓
 + Drug B ✓

① Dropouts ? Treatment →

who fails to complete

② missing value



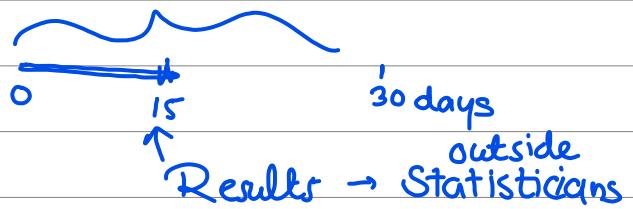
③ gmat → Premature Termination.
 ④ 7 pre



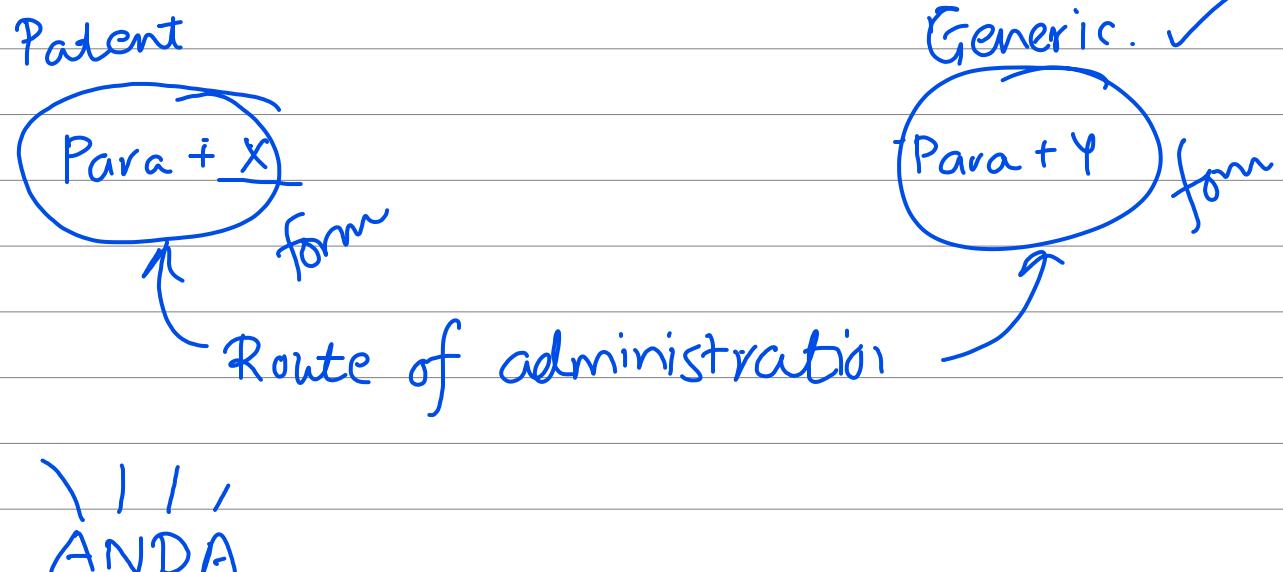
* Multicenter Trials :- ?

- 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
 = 20 students Thank you.



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

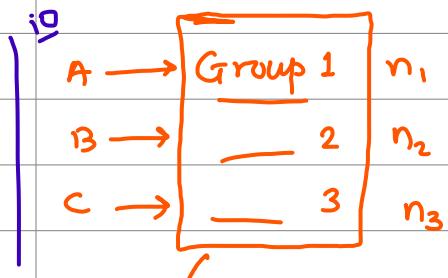
A.	<u>1, 4</u>	2
B.	2, 5, 8	3
C	3, 6, 7	3

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

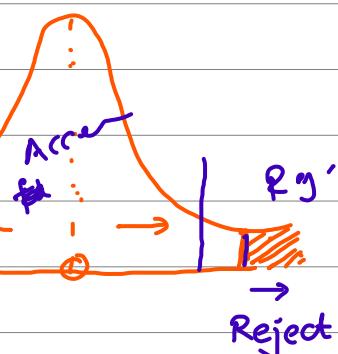
$$\checkmark \mu_A = \mu_B = \mu_C$$

p value

$$p < \alpha$$

↳ Reject H₀

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



Post-hoc

Pairwise Comparison

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

$$\textcircled{1} \quad \mu_A = \mu_B$$

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

$$\textcircled{3} \quad \mu_B = \mu_C$$

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

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

Bonferroni / Tukey
t-test

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

② Two-way

Two factors - different levels

① Smoking habits

②

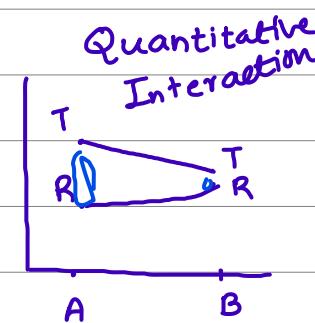
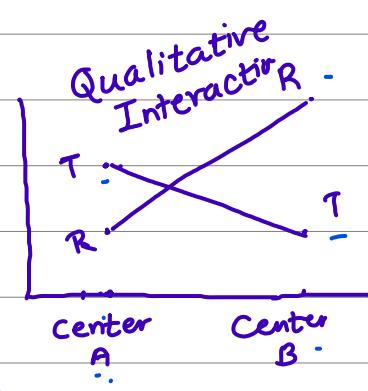
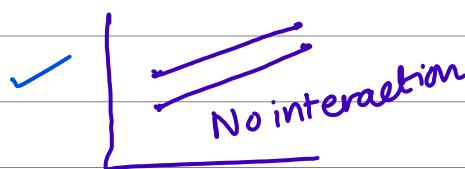
	Smoker	Non smoker
low	n_1	n_2
Moderate		
high		



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

error \rightarrow $n-r.c$

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

Interaction

effect identify

Confounding ?

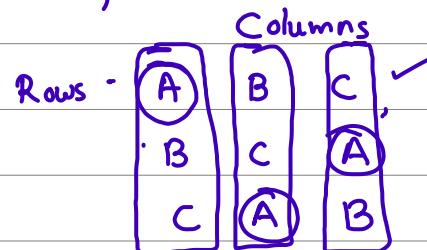
- due to some identified/unidentified factor effect

CRD RBD
1 2 3 Factorial

LSD

Latin Square Design

3 factors



A	B1	C1	B2	C2	A2
B	C	A			
C	A1	B1			

Balanced Incomplete Block Design

Designs CT

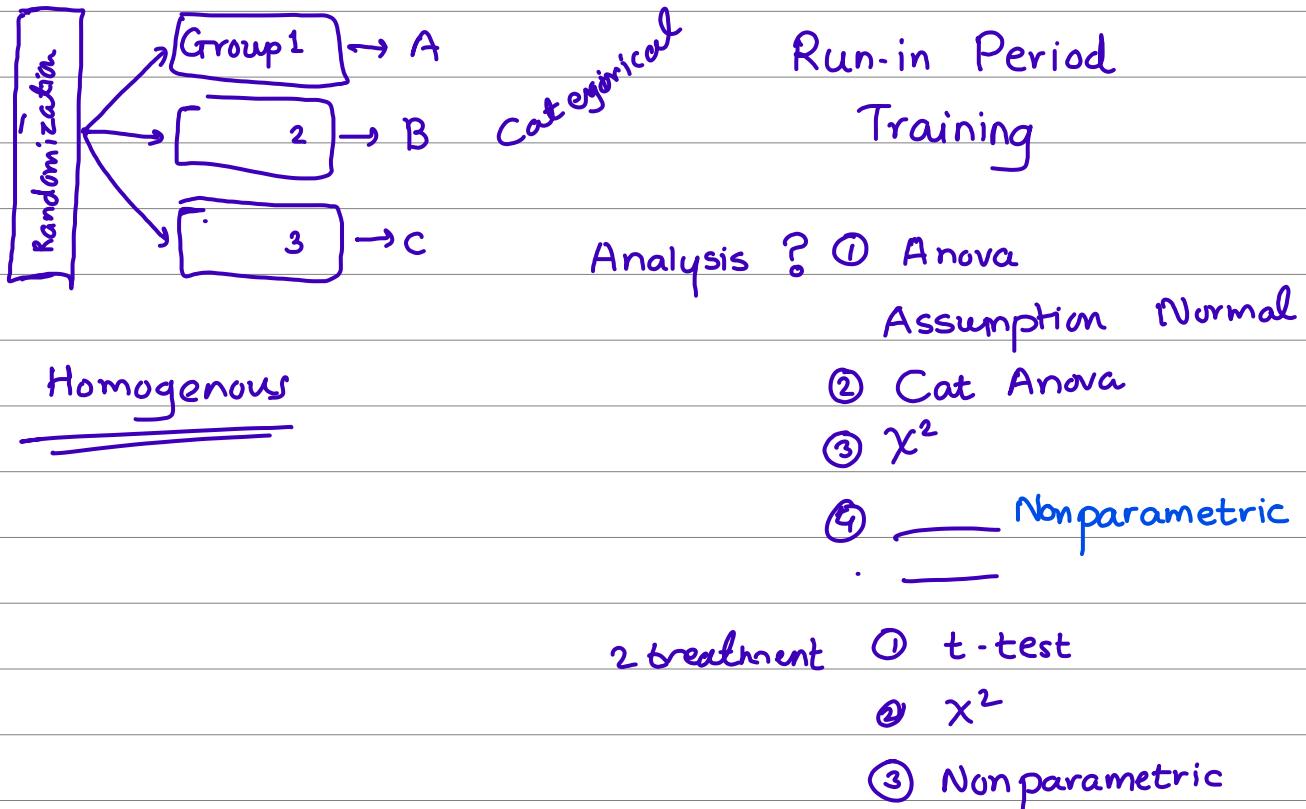
Obs: ① Test treat > better
Refere

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

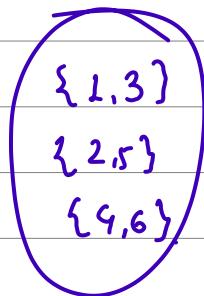
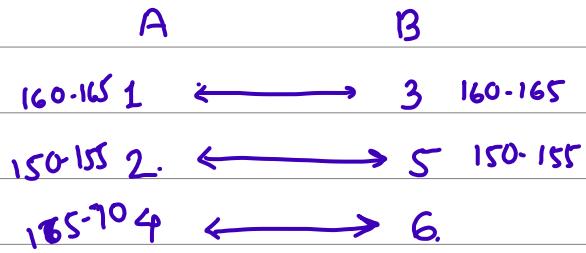
Control :-

Active Concurrent Controls

* Parallel Group Design 3 treatment A, B, C



Matched Pair



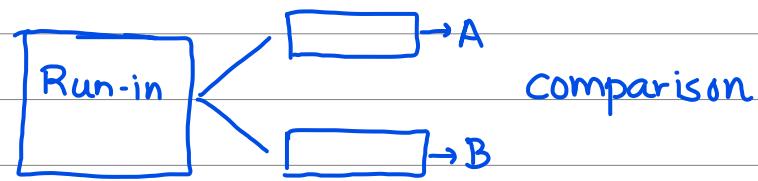
Abs : 4, 6, 9, 10, 13-14, 16, 22, . 30, 33-35, 39, 43-47, 50, 51, 53-55 = Total present 37

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

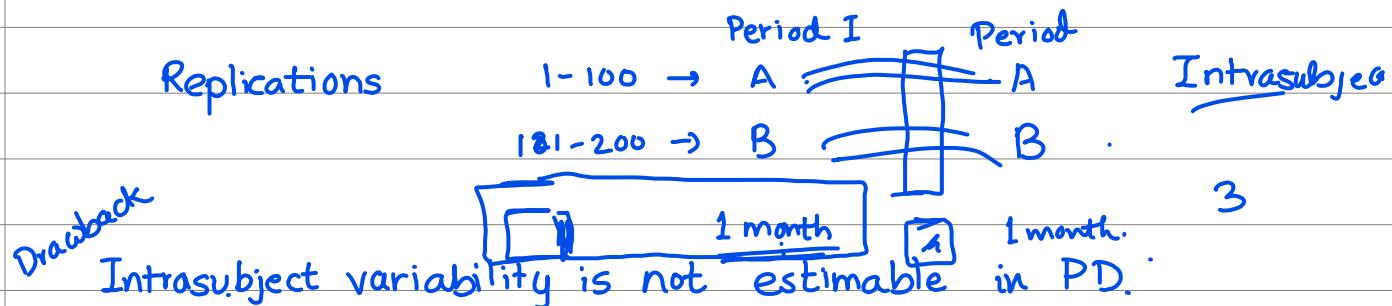
Variability \rightarrow Intersubject :- Same Single treatment \rightarrow diff sub \rightarrow diff responses variation.

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

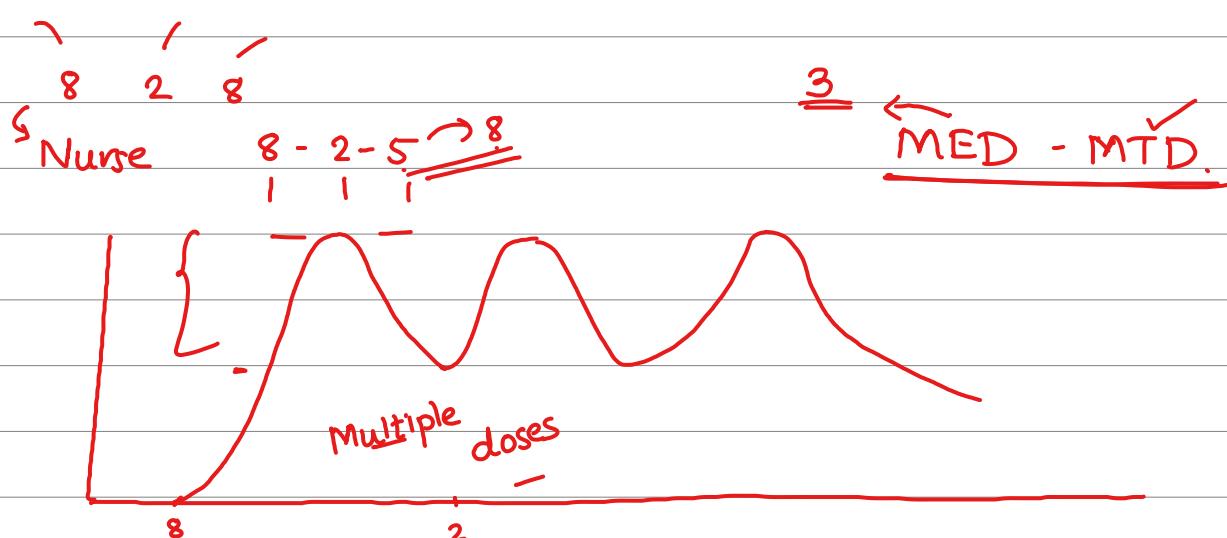
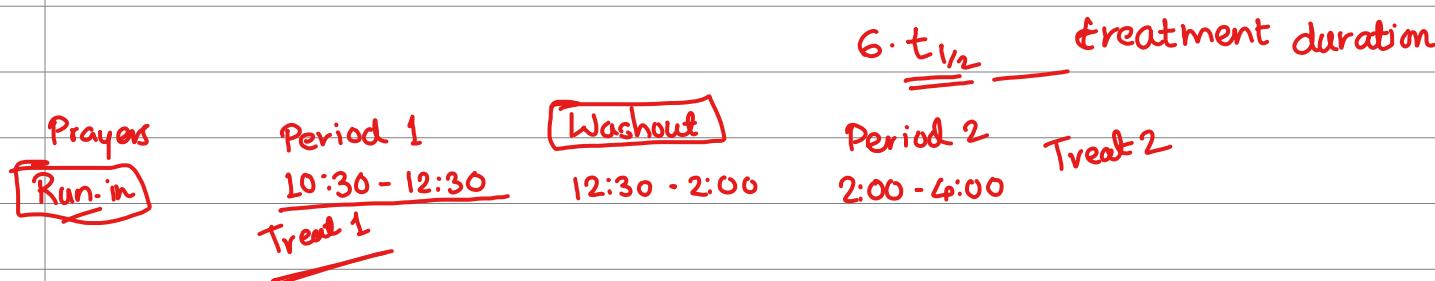
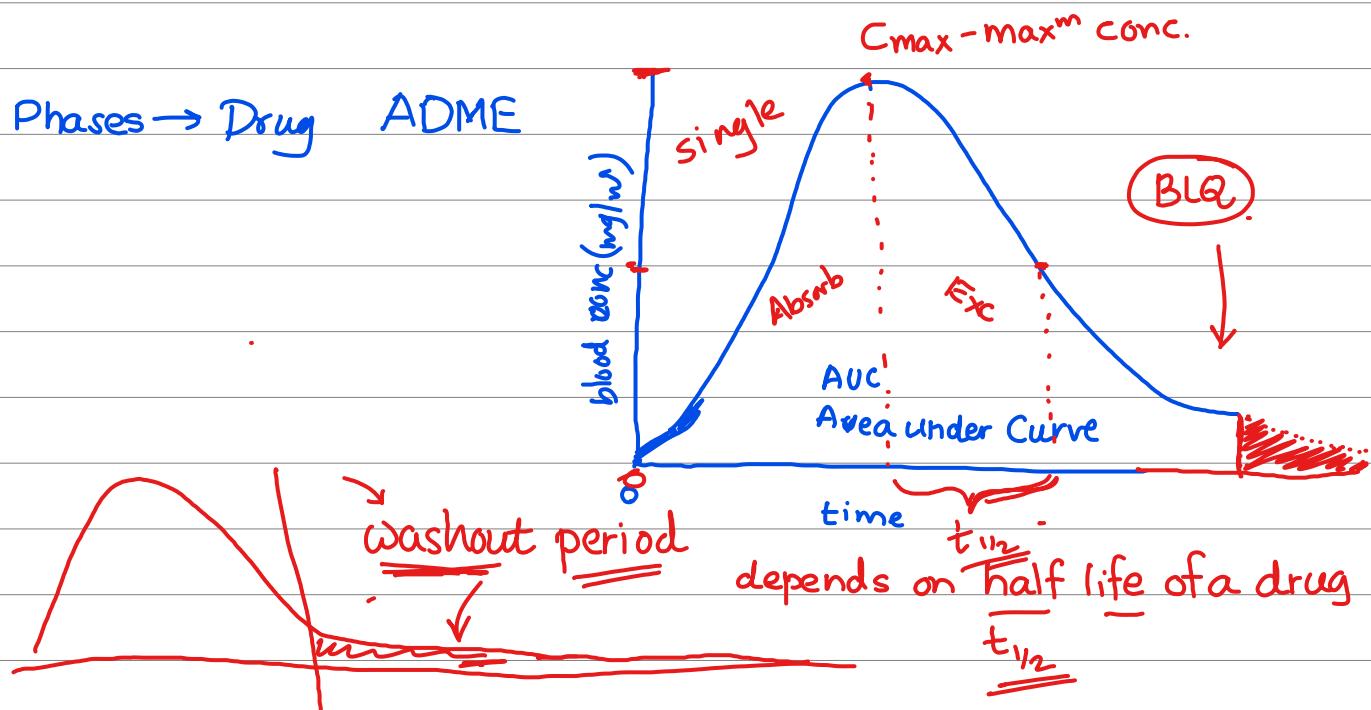
⑤ Washout period

for previous treat



② 8 10 12 2 4

8 10 12 2



Treatment Effect

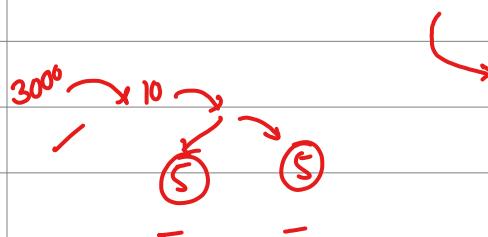
① Active ingredient] X I

② Placebo

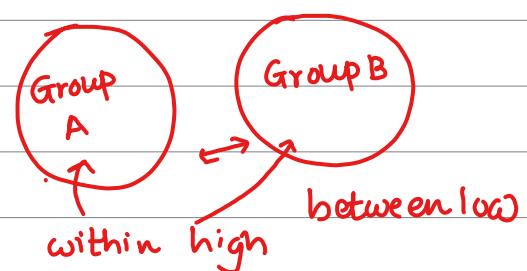
③ Disease] ✓

④ Other factor] ✓

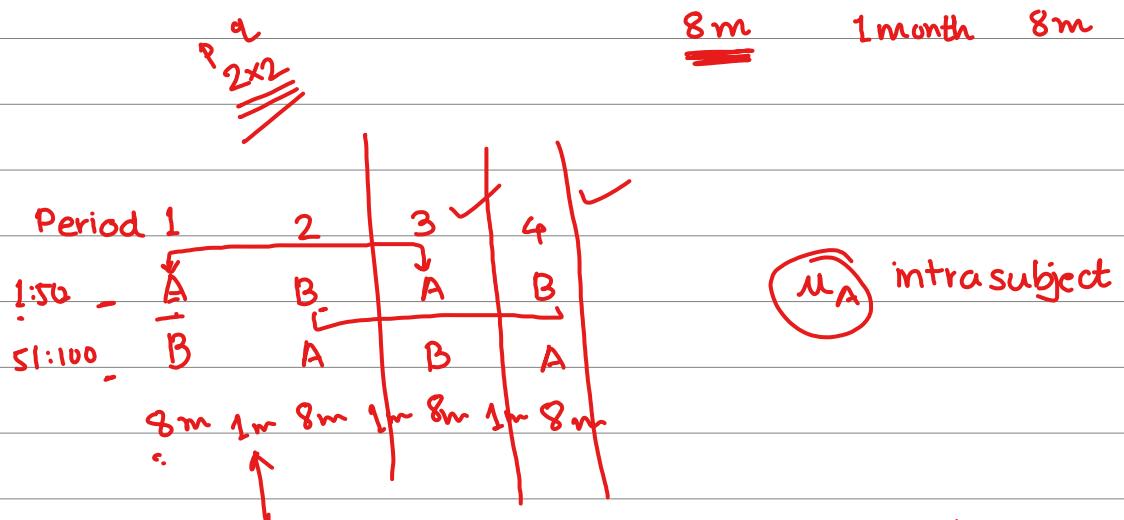
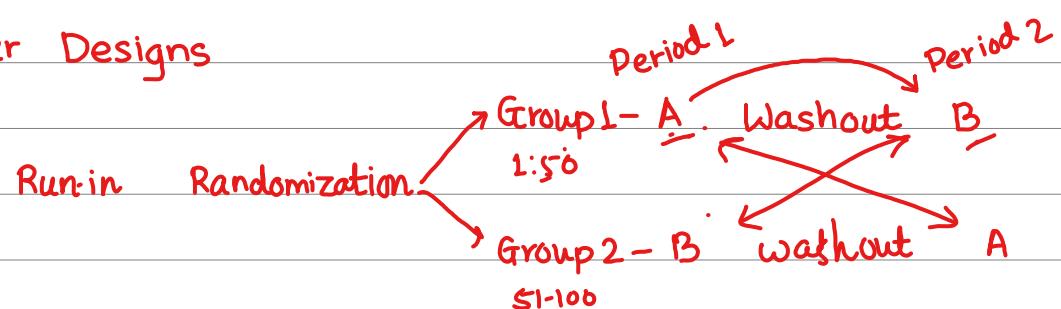
✓ Cluster Randomized design



ST-103
Cluster Sampling ?



Cross-over Designs



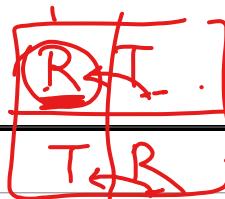
Complete Crossover

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 n period



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

general mean effect
subject period seq.
Random washout period = Random

Summer		Winter	
Period 1, j=1		Period 2, j=2	
$E(Y_{11}) = \mu + F_R + P_1$		$E(Y_{21}) = \mu + F_T + C_R + P_2$	1: n_1 n_K
$E(Y_{12}) = \mu + F_T + P_1$		$E(Y_{22}) = \mu + F_R + C_T + P_2$	1: n_2
$E(\bar{Y}_{12} - \bar{Y}_{11}) = F_T - F_R$		$E(\bar{Y}_{22} - \bar{Y}_{21}) = F_R - F_T + C_T - C_R$	
Seq 1 $\Rightarrow K=1$		Seq 2 $\Rightarrow K=2$	
2x2		Random Effect Models	Fixed effect Models
add	E	$F_R - F_T + C_T - C_R - F_T + F_R \Rightarrow 2(F_R - F_T) + (C_T - C_R)$	✓

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

fixed Random

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

Random

$$P_1 + P_2 = 0, \quad C_R + C_T = 0,$$

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

$$F_R + F_T = 0$$

$$\epsilon_{ijk} \sim N(0, \sigma_e^2)$$

i.i.d.

 S_{ik}, ϵ_{ijk} indep.

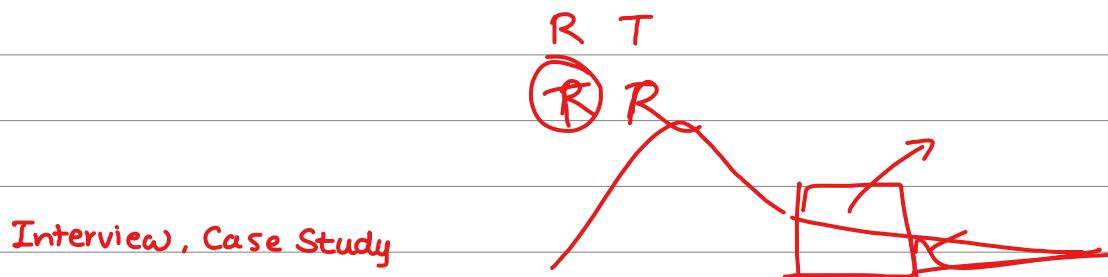
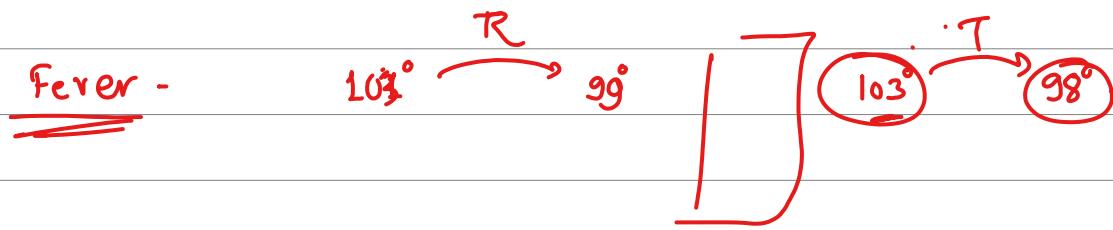
~~$F_R \neq T$~~ $C_T - C_R$ = Carryover effect -

$$-(\bar{Y}_{12} - \bar{Y}_{11}) + (\bar{Y}_{22} - \bar{Y}_{21}) \quad \text{period seq} \quad = C_T - C_R$$

Cross-over design

p x q

If Carryover effect is not zero, we have to ignore period II.



Absent: $2003, 6, 9, 10, 15-17, 25, 30, 35, 39, 43-47, 51, \dots = 38$

	PL	P2
G 1	A	B
G 2	B	A

① Std. Crossover designs

1	A	B	C
2	B	C	A
3	C	A	B

Std.
3x3 Crossover design

seqⁿ \downarrow no. of periods
 $p \times q$
 $\underline{p=q}$

Higher order crossover design

$p \times q$ no. of treatments
 t

① Treatments:- A & B $t=2$

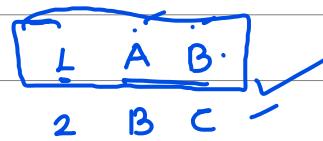
ei: $p>t$ or $q>t$

1	A	-	2	3	\leftarrow $q=3$
2	B	-	B	B	\leftarrow $p=2$
		-	A	A	$\underline{2 \times 3}$ $t \geq 2$

1	A	B	2	3	\leftarrow
2	B	A			
3	A	B			$\underline{3 \times 2}$

Sik \Rightarrow

3 treatment



contrast? 3 C A ✓

$$\begin{aligned}\hat{\mu}_A - \hat{\mu}_B &= 0 \\ \hat{\mu}_B - \hat{\mu}_C &= 0 \\ \hat{\mu}_C - \hat{\mu}_A &= 0\end{aligned}$$

✓ balanced variance (Same)
↳ Balanced design

Williams

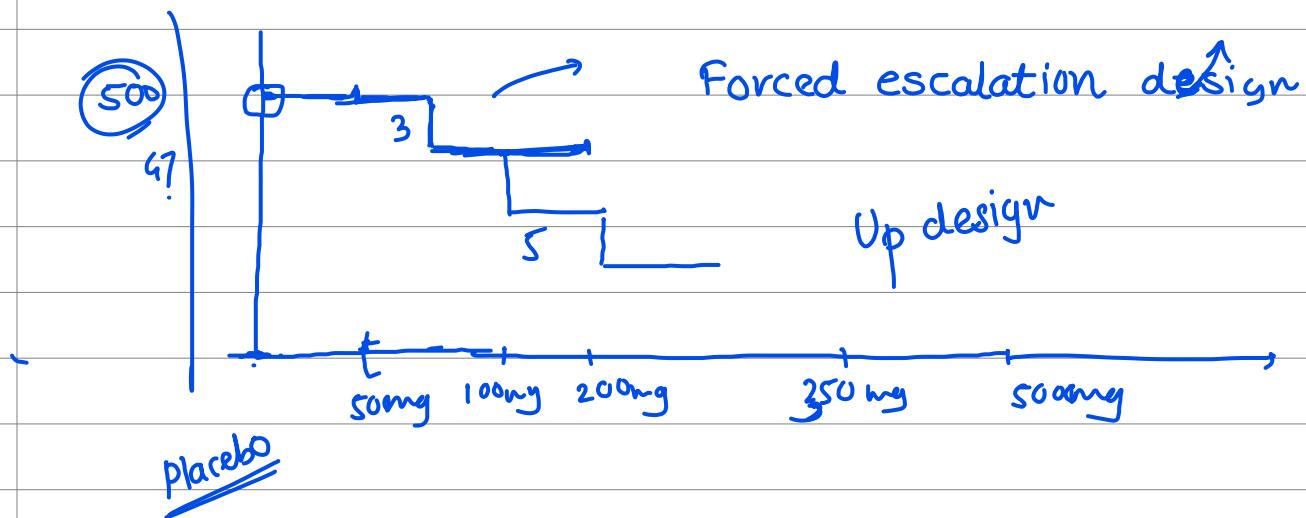
A BCD
B C DA
C DA B
D A B C

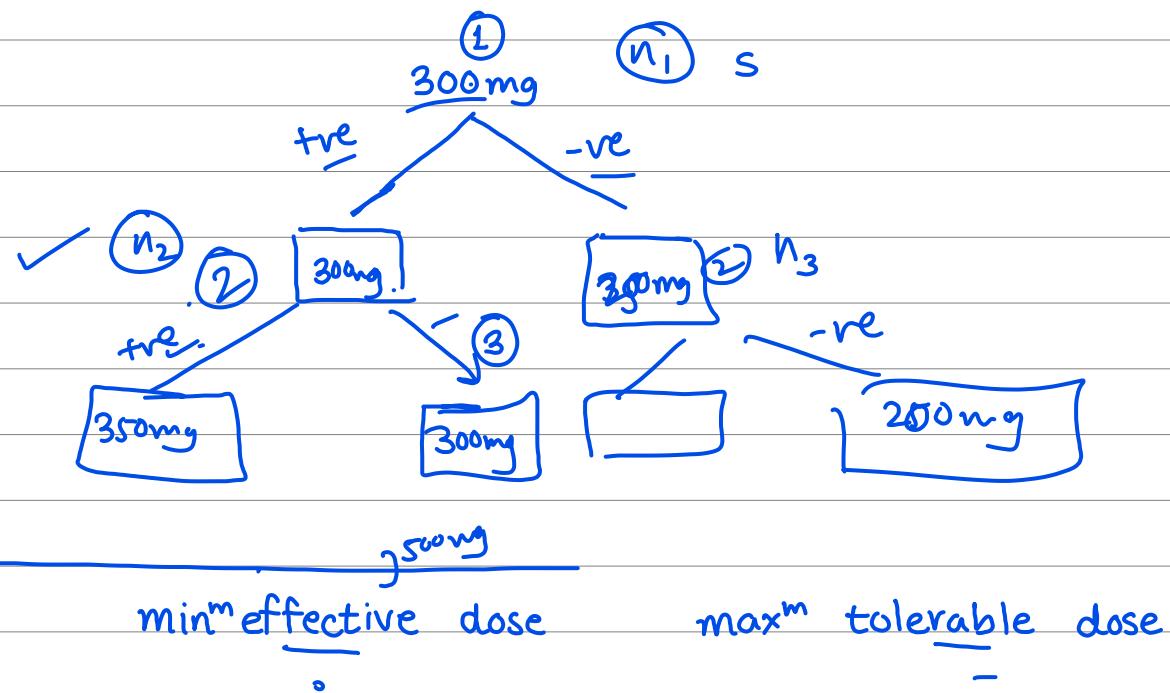
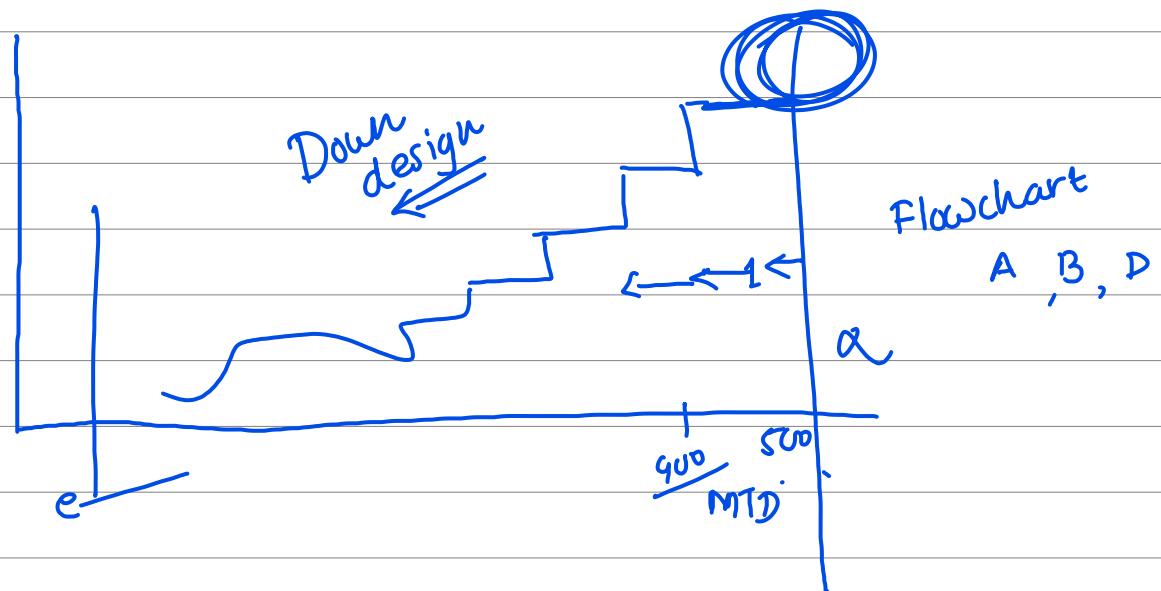
Titration Designs

Phase-I trials safety- evaluation

II

Titration. Therapeutic window [MED - MTD]





Dose- Response ~~Pre~~ Trials

① Parallel Dose Response

② Crossover

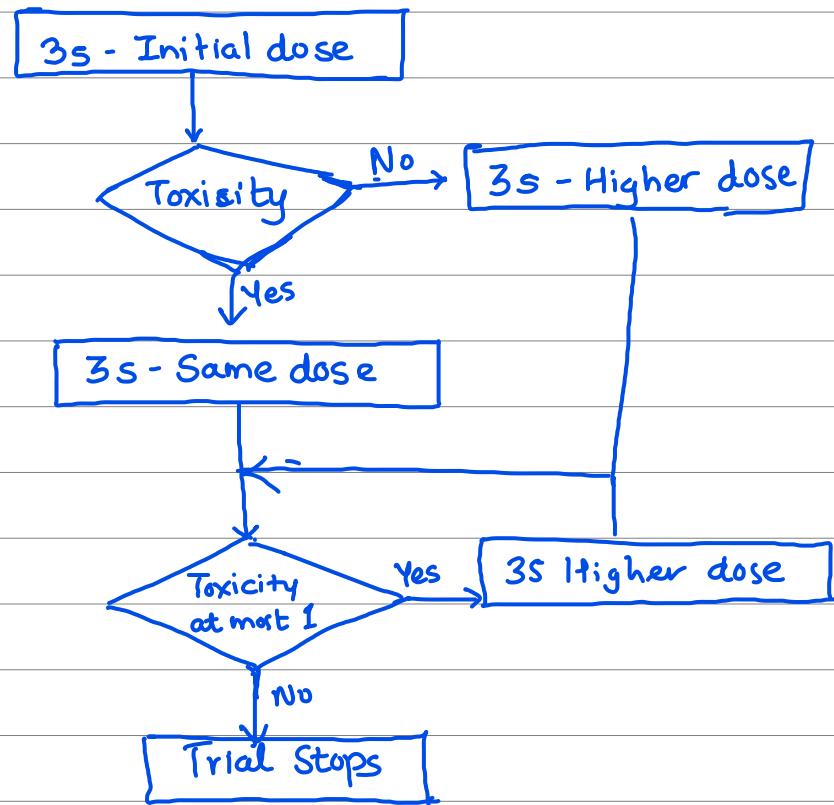
③ forced Titration

④ Optional Titration

Absent :- 6; 15-17, 24, 25, 33-35, 39-41, 43-45, 47, 50, 55

Flowchart A Design A

Up ↑

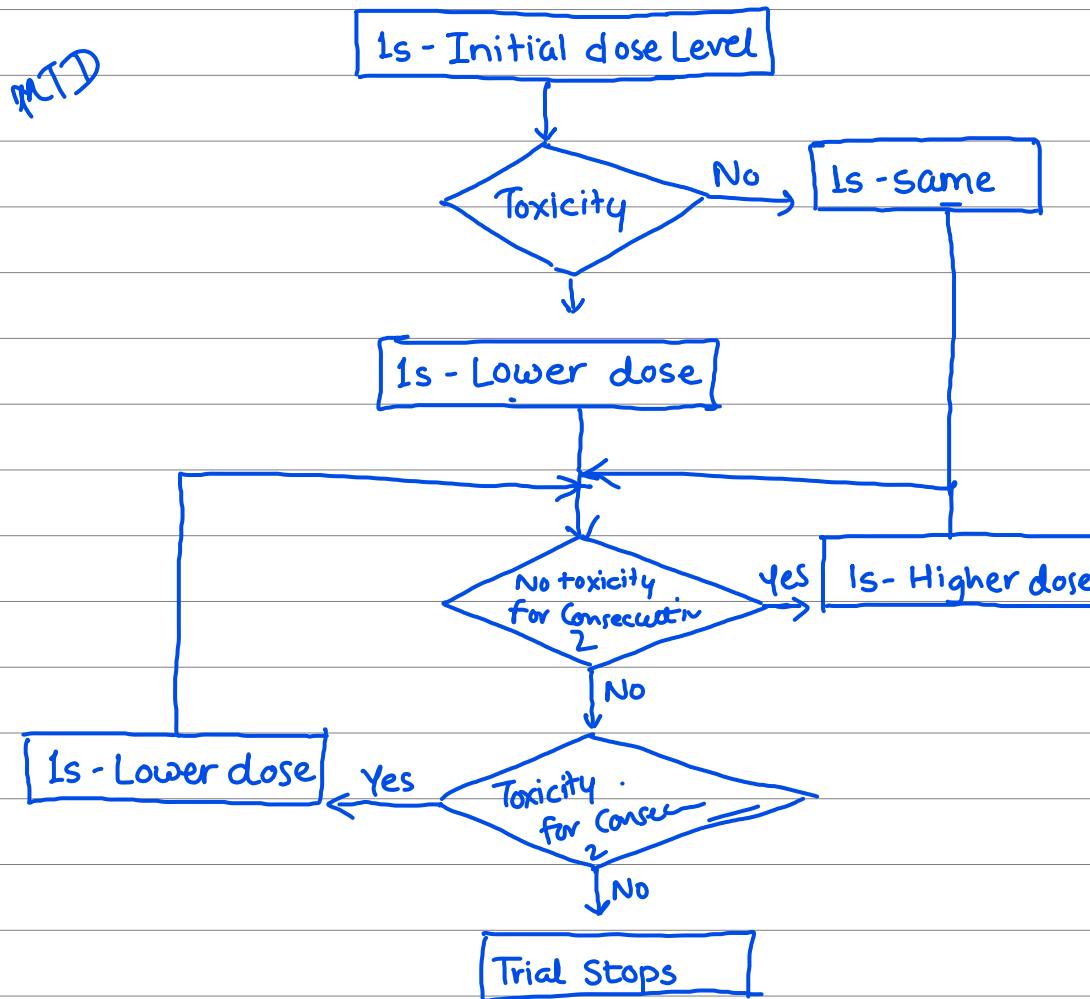


Flow

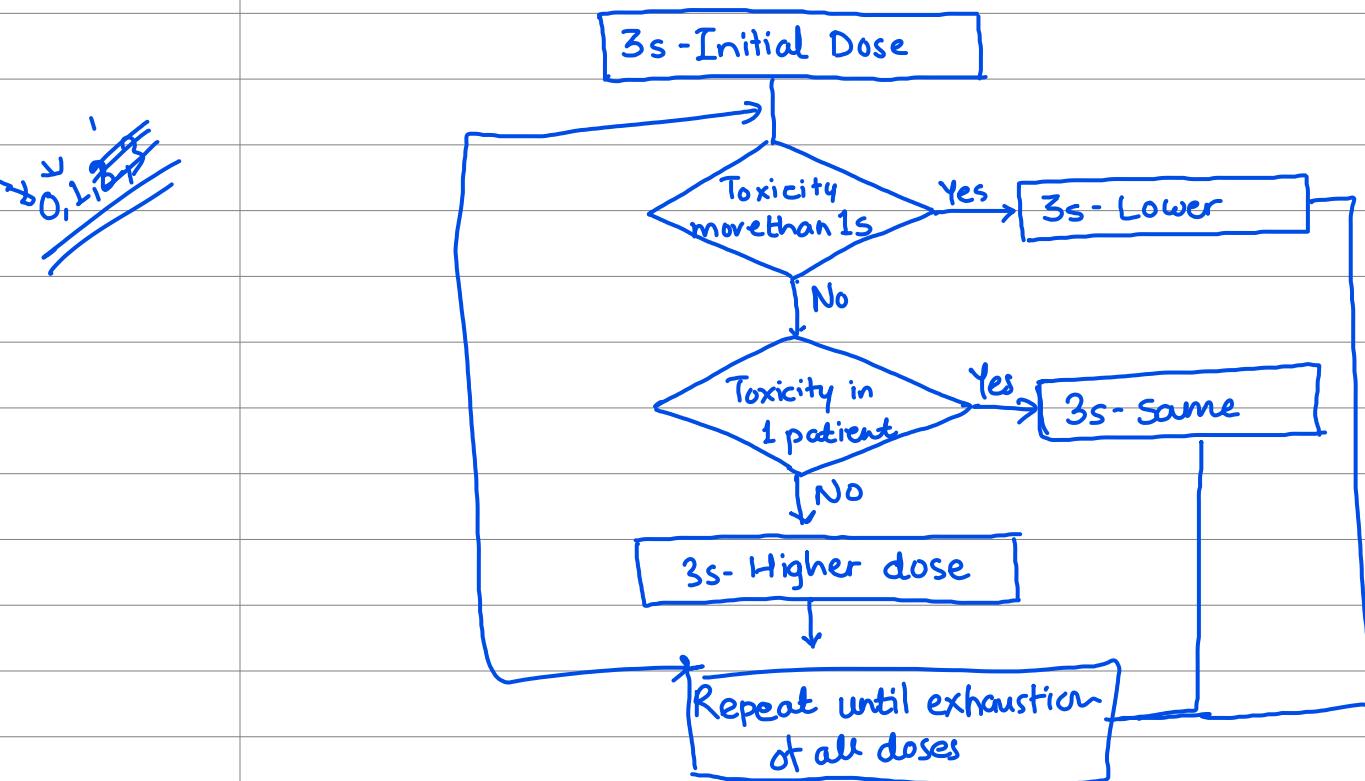
~~MED~~

Flowchart For Design B

down ↓



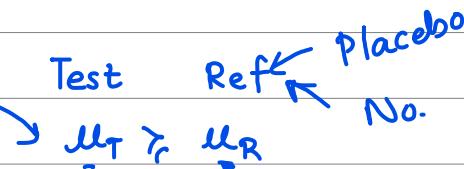
Flowchart for Design D :-



Classification of CTs

① Multicenter Trials :-

② Superiority Trials :-



③ Active control :-

$$\mu_T > \mu_A \quad \text{active drug}$$

Non-superiority \rightarrow Equivalence trial

$$\mu_T = \mu_A$$

\rightarrow Variance Bioequivalence ✓
 \rightarrow Average Bioequivalence ✓

④ Dose-Response Trials :-

↳ ① Randomised Parallel Dose Design

② Cross over Dose Response

③ Forced titration dose-escalation

④ Placebo-controlled

⑤ Combination Trials :-

↳ Combination of active ingredients.

⑥ Vaccine ?

↳ ① Superiority Immunogen trial

② Dose-Res I

③ Cro

④

⑤

① Multicenter Trials ?

Why? i) Generalization -

ii) Treatment by center interaction ✓

iii) Sample size

① Generalization

i) Subject Recruitment

Rare - Brain-tumor - 20-25.

- ① -
 - ② -
 - ③ -
- sample size →

estimator
comparable group.

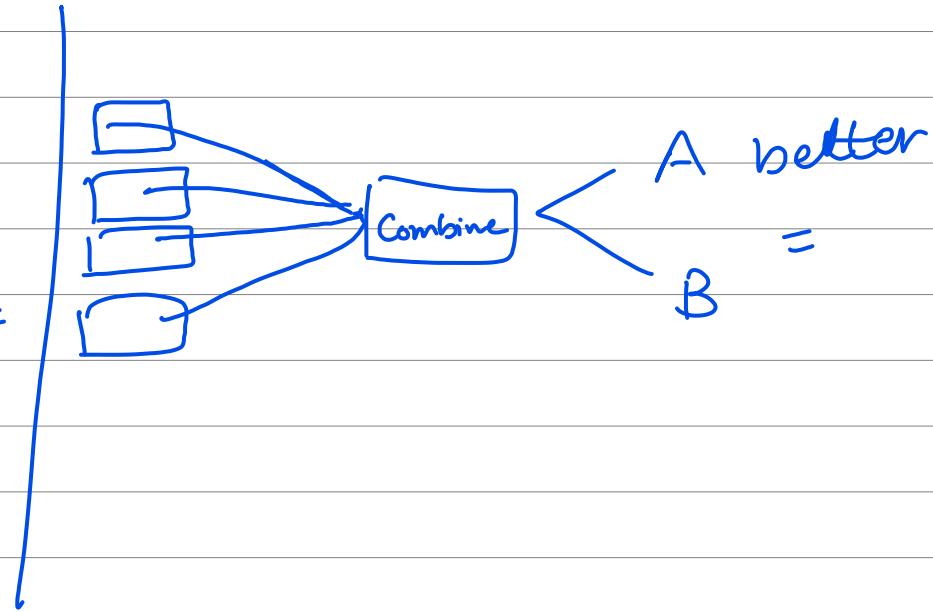
② Homogenous

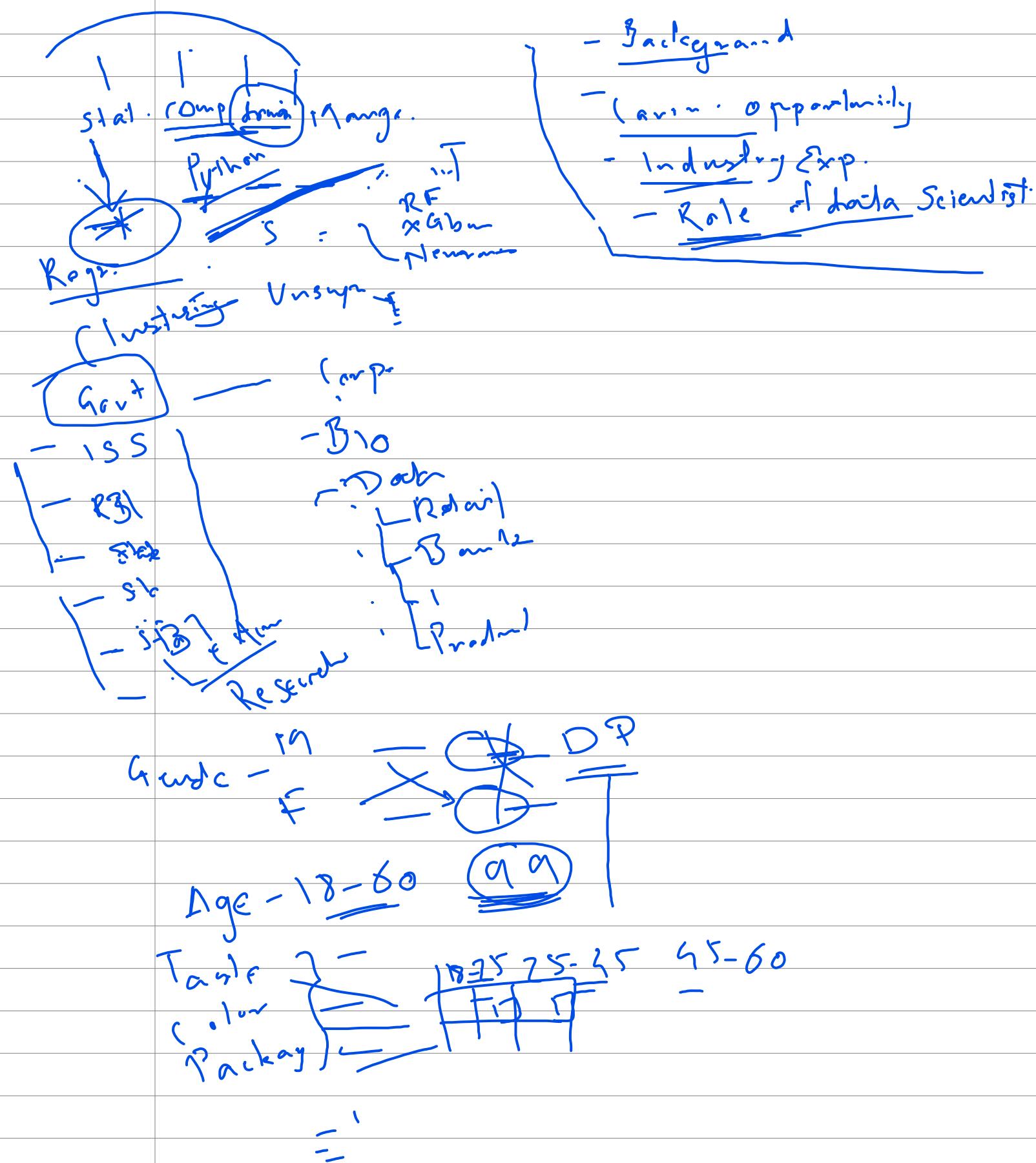
Multicenter:

Center Better

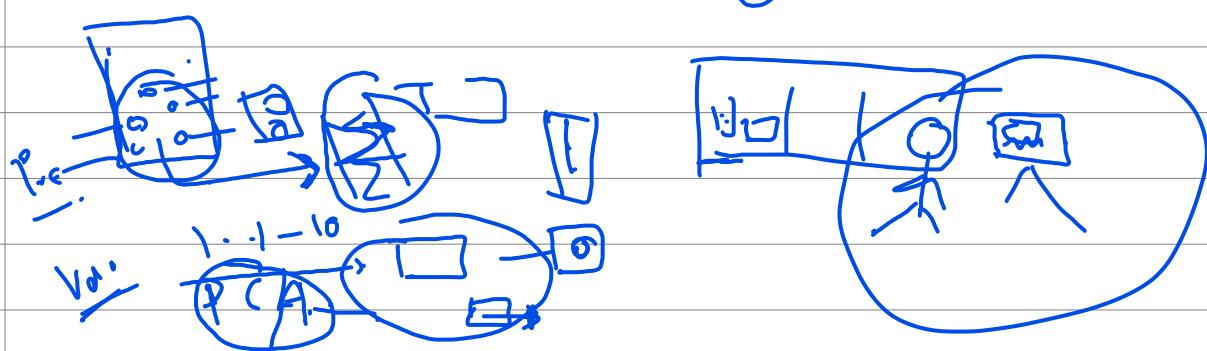
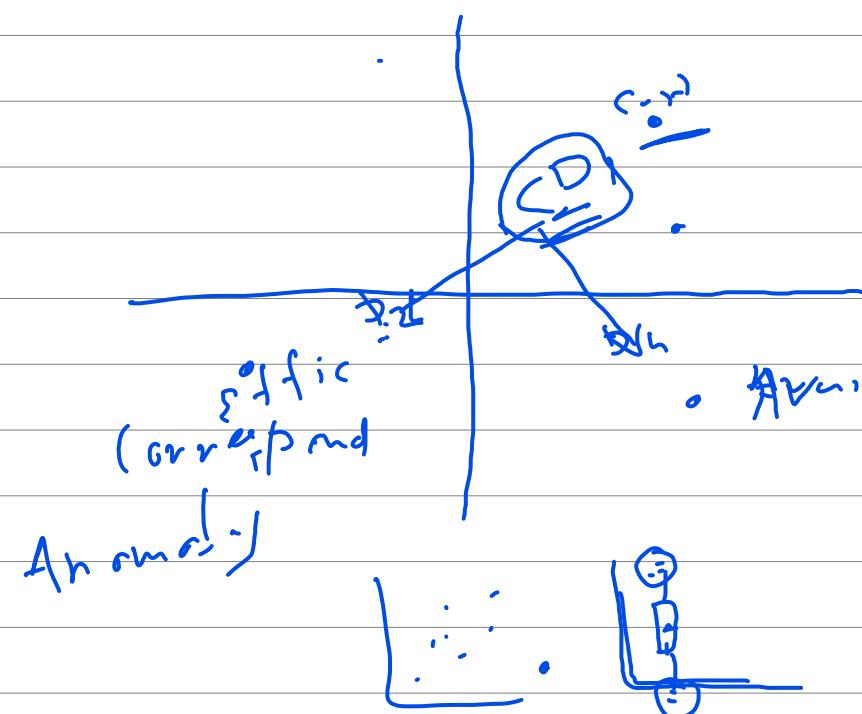
- 1 → A -
- 2 → A -
- 3 → B - 3/4
- 4 → A - =

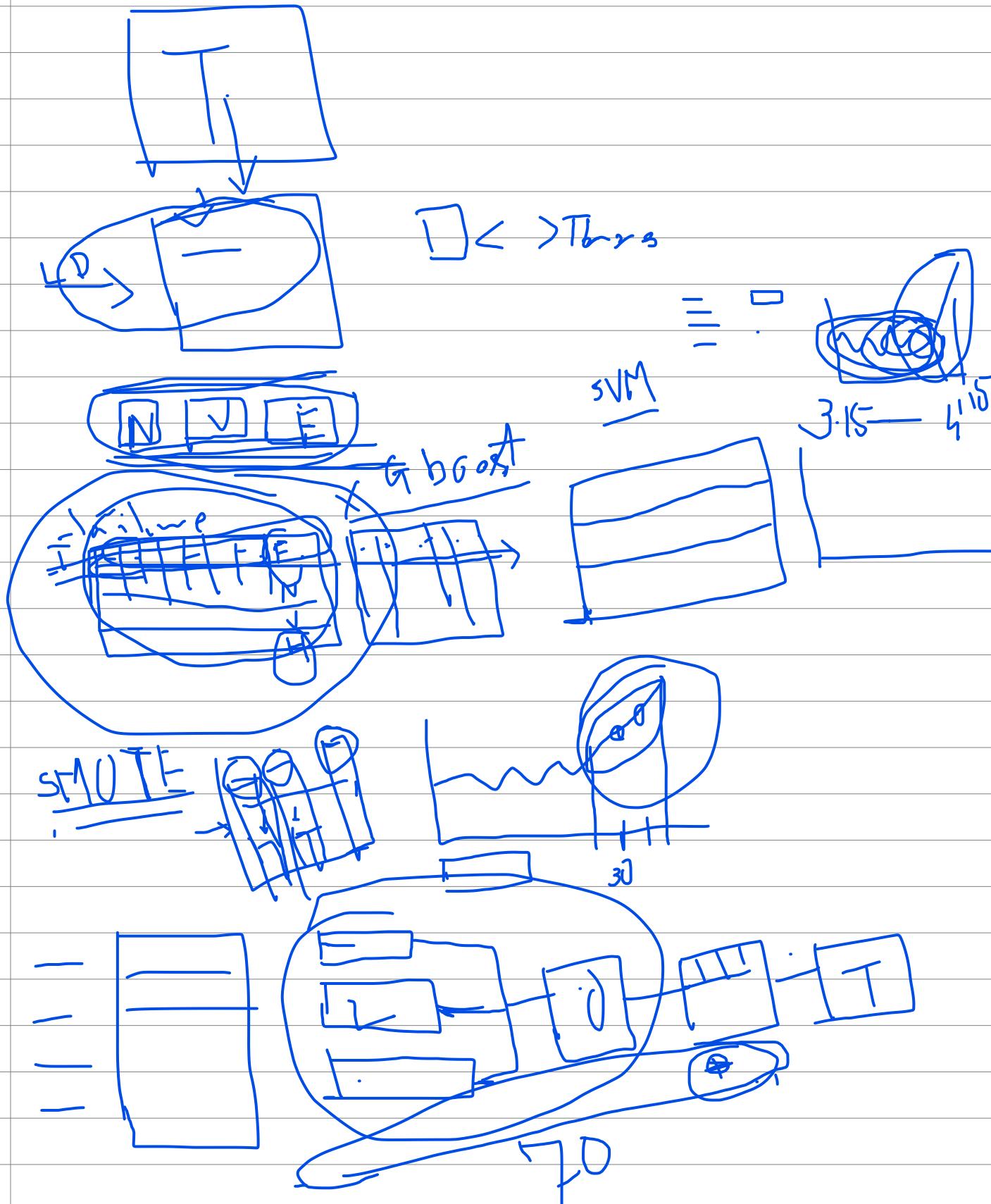
(A)

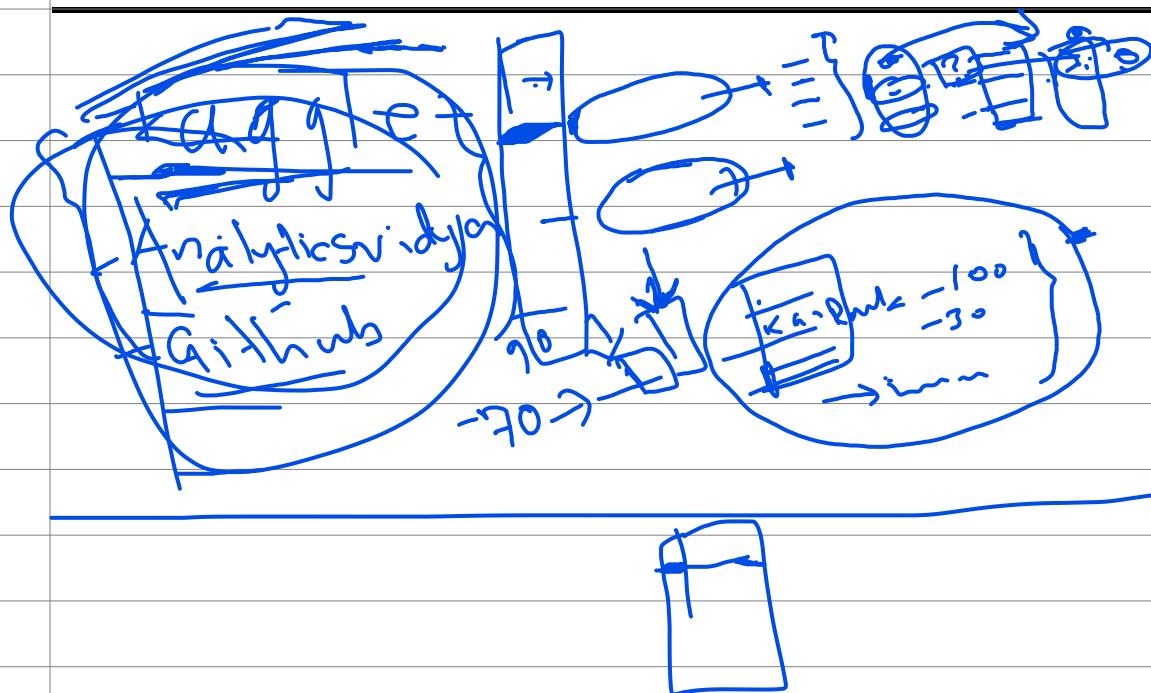




	cost	mail	fr.		
-CD	1	2	5	1-5	
-D1	3	5	5		
-D2					
-D3					
-D4					







d

EE
-
-

Knowledge Transfer

