

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

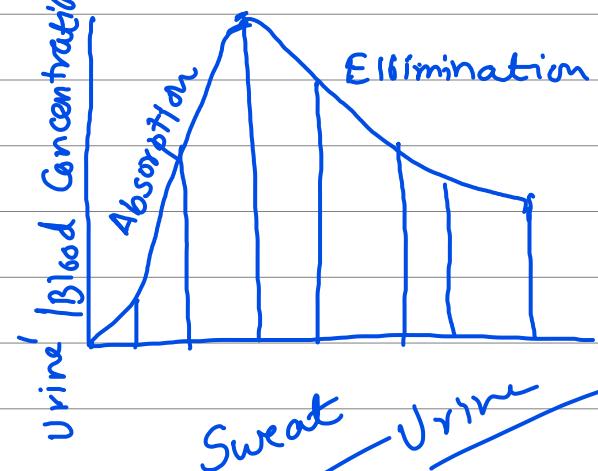
Pharmacology

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

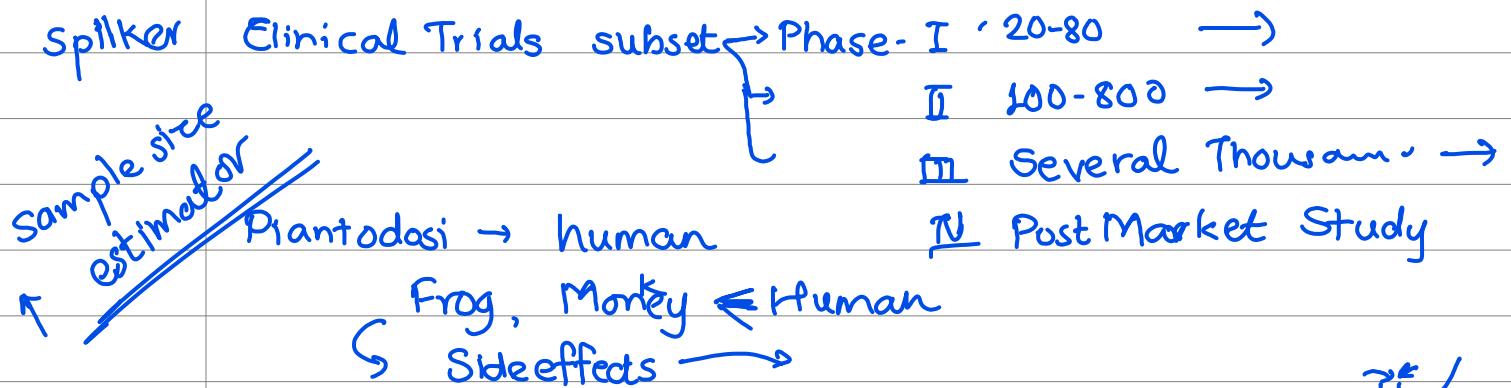
$P(\text{Death})$ Fund \rightarrow
 $\text{due to } x$ \rightarrow 0.0001

Phase-I
Life threatening
side effects

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

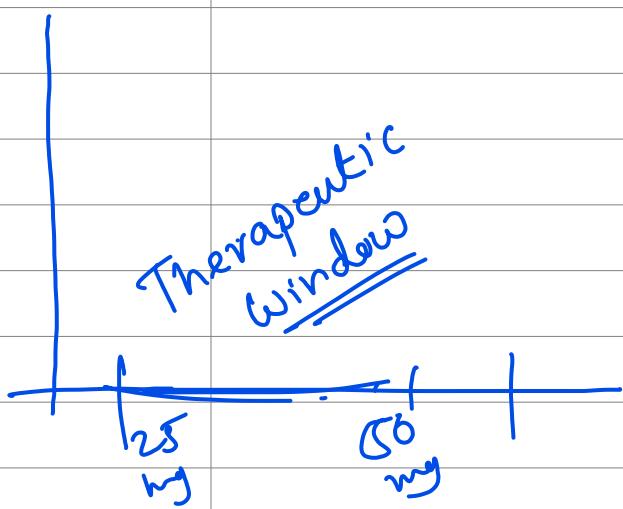
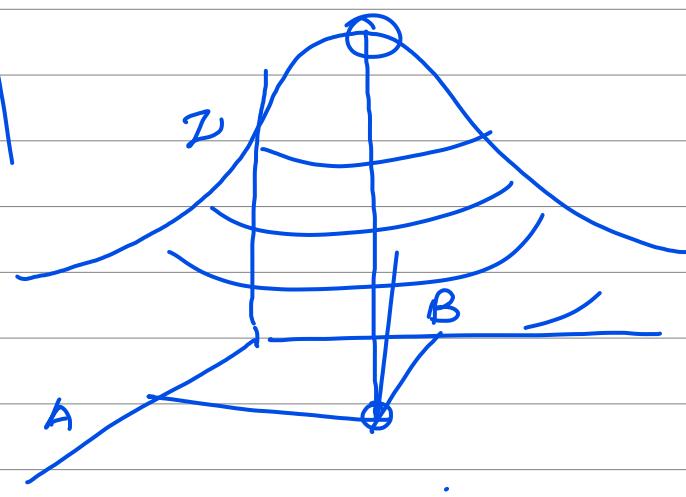
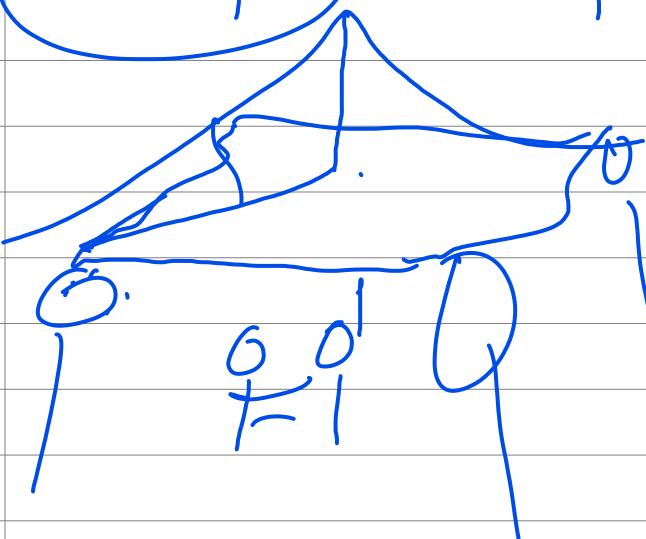
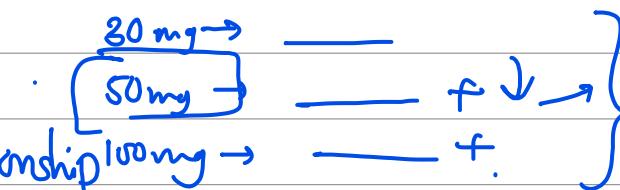
$\rightarrow 800 - 1000 \rightarrow$ effectiveness side effect

\rightarrow Thousands \rightarrow Physicians labelling
IV = 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

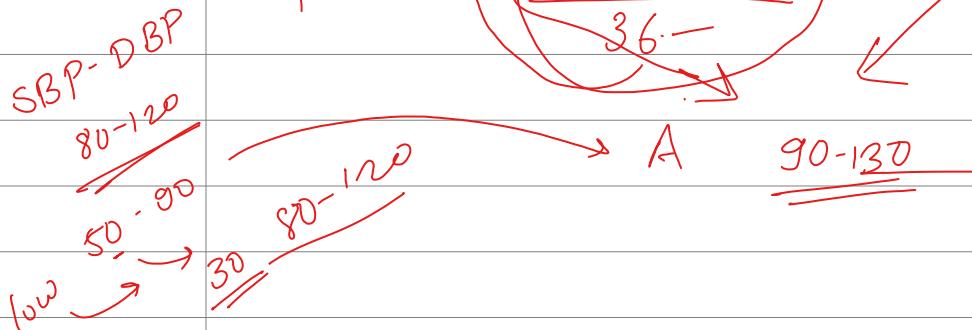
Clinical diff

C_p ?

UST - LSL

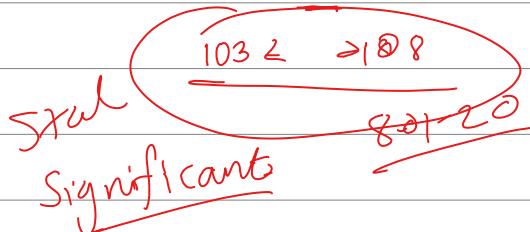
LSL ? USL ?

Clinician / Doctors



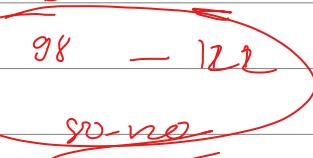
$$A \rightarrow \mu_A = 105$$

$$\delta_A = 1$$

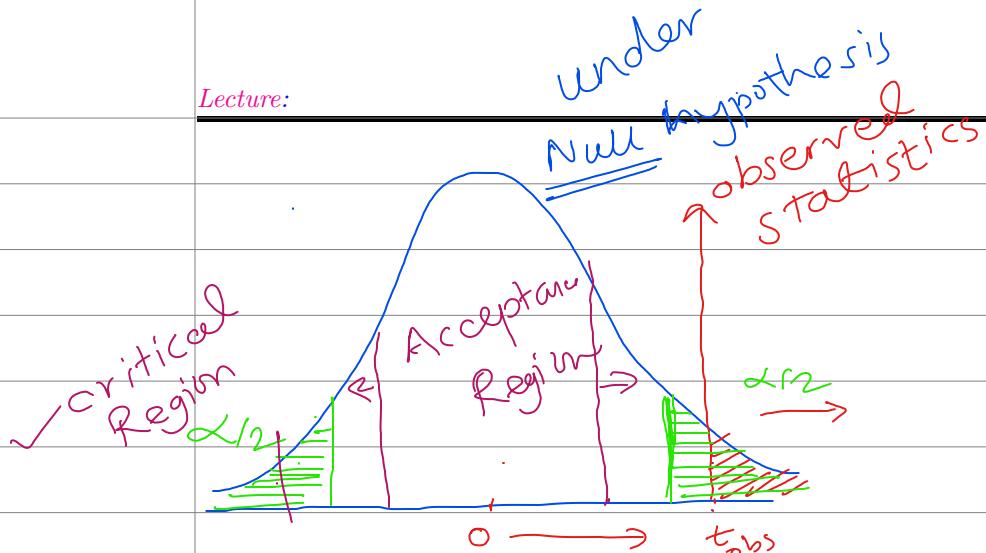


$$B = \mu_B = 110$$

$$\delta_B = 2$$



Clinician



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

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

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

Confusion
Rohan Sir

Patent

Trademark filed (Branded)

Active ingredient (x)

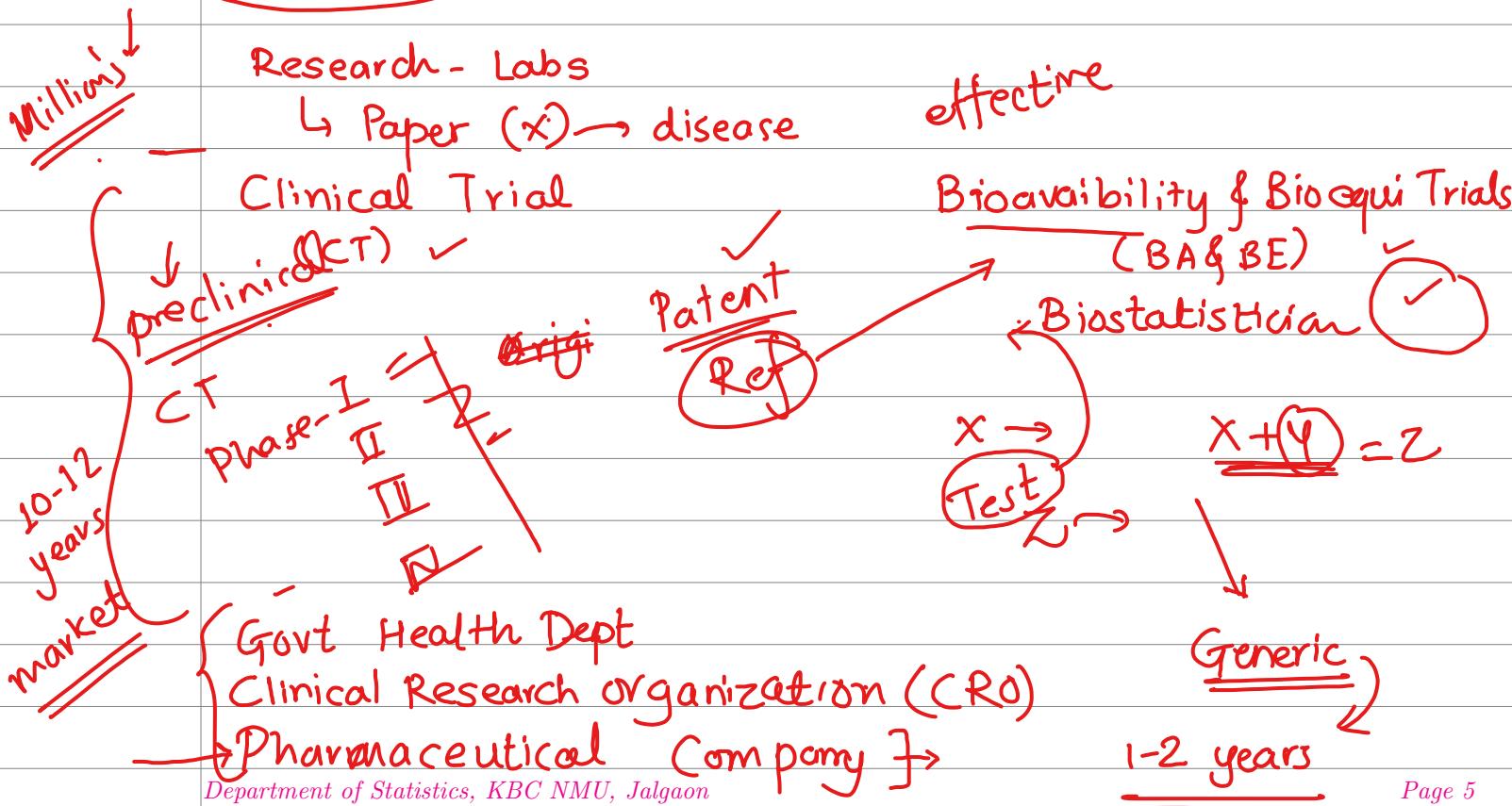
Inactive ingre

Generic Drug

Copied -

→ same (x)

→ different



BA - BE
patent → generic

→ Same dosage
Strength
Safety
Route of administration



Non comm IND

① Sponsors → Physician → Govt → NARI → CRO → TCR → Pharma Co.

② Market Research

③ ADA

Objective

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

Objectives

①	—	—	✓
②	—	—	✓
③	—	—	✓
④	—	—	—

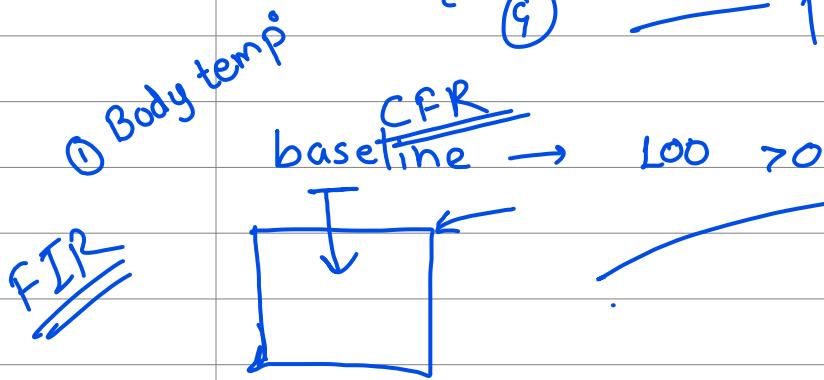
Objectives

①	—	—	✓
②	—	—	✓
③	—	—	✓
④	—	—	—

Objectives

①	—	—	✓
②	—	—	✓
③	—	—	✓
④	—	—	—

Fever ↓
Cold ↓
Sweat ↓



effective or not
clinical endpoint
≤ 100

Hypothesis.

Lecture:

Manoj C Patil

$$\textcircled{1} \quad H_0: \mu_T > 100$$

$$H_1: \mu_T \leq 100$$

example

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

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

Inclusion & Exclusion

Inclusion & Exclusion for CTs

① < 18 & ≥ 60 old age Exclude

② Feeding mother / pregnant

③ History disease

Medications

④ _____

⑤ _____

Inclusion
Some

Disease.

Healthy volunteer

③ > 18

④ _____

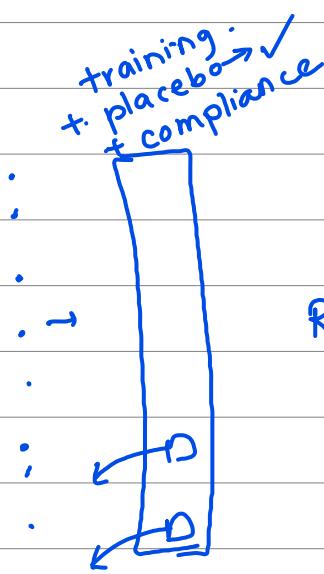
⑤ _____

Some inclusion & all exclusion criteria
follow
not followed

Run-in Period

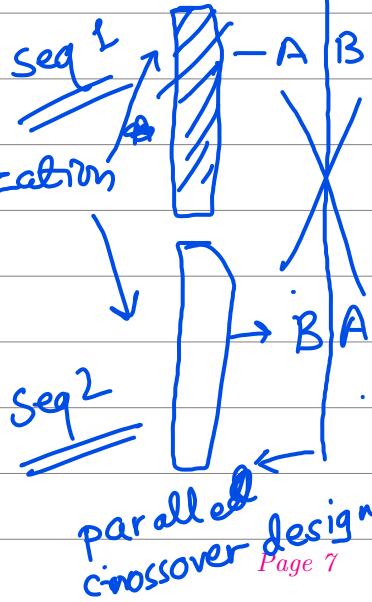
inclusion &
exclusion
criteria

Titration
design



+ training
+ placebo
+ compliance

Randomization



parallel
crossover design

?

Titration design - ①

②

③

④

⑤

⑥

Upward

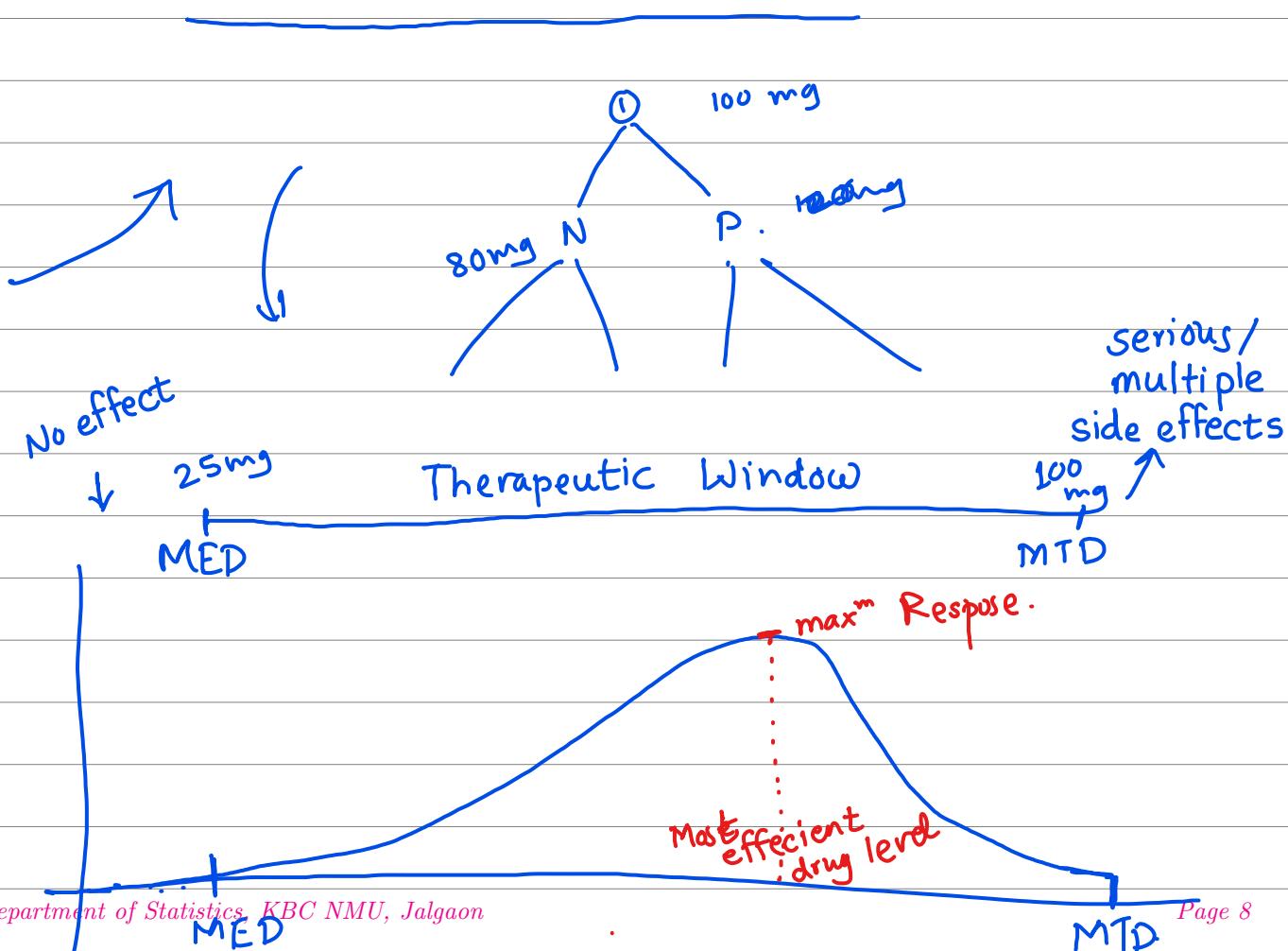
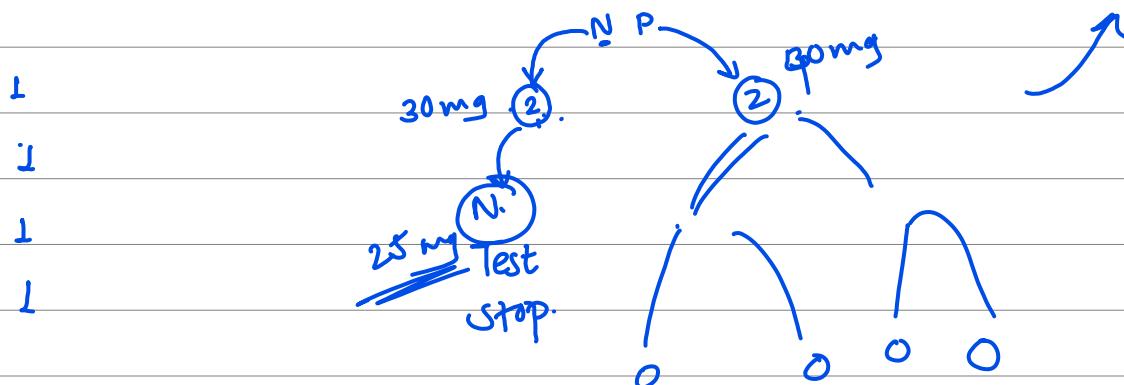
Upward-downward

downward

Human

Safety

① . 30mg -



① Methods of blinding

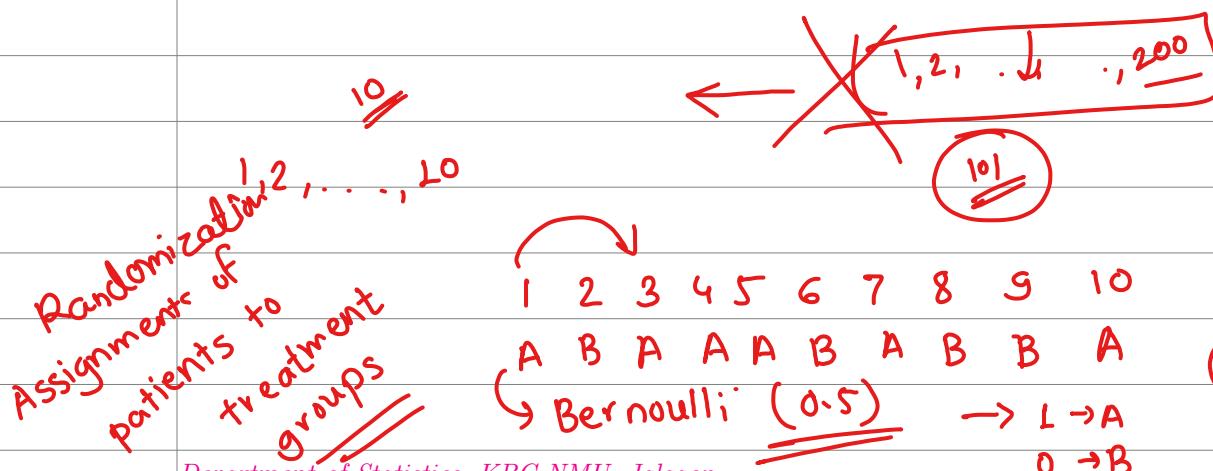
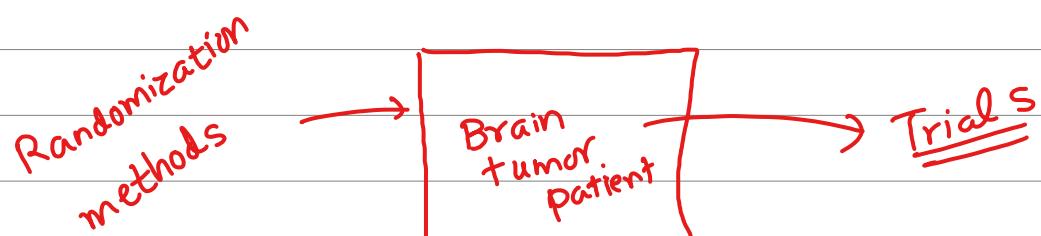
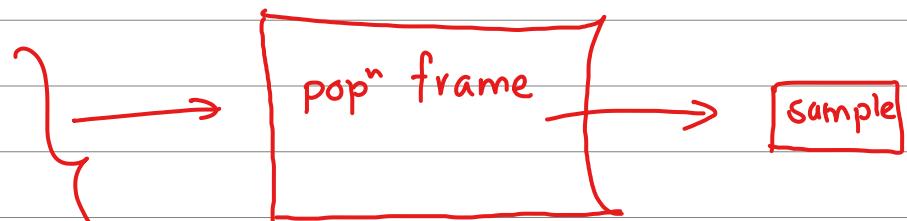
- open label** ① No - Everyone knows
- ② Single - Patient / Dr. any one is blinded
- ③ Double - & no one knows the allocations
- ④ Triple - Patient / Dr / Other staff all are blinded
↳ Data collectors - Nurse

Data Analysts - Statisticians



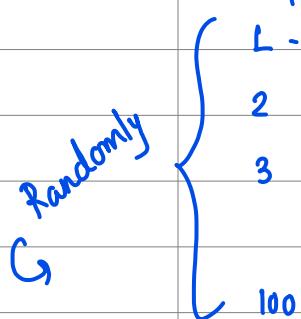
* Randomization ✓

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



① Complete Randomization

drugs
A & B assign with equal prob.

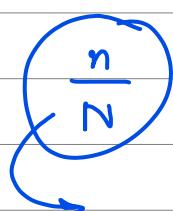


using R → SRSWR

① sample

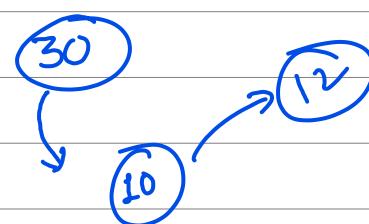
② Bernoulli: — $0.5 \rightarrow L \rightarrow A$
 $0 \rightarrow B$

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 ✓

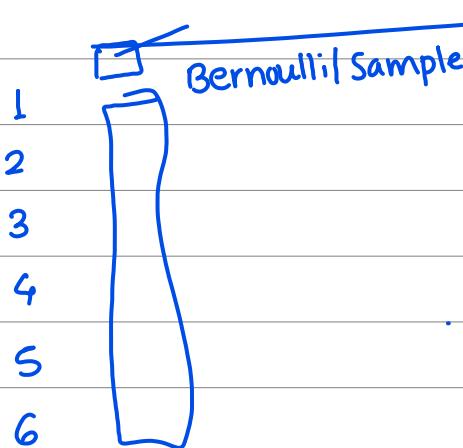
A 1 4 6 ✓ $n(A) = 3$

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	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	9	B	20	10	30	10

Permutation of 1: blocksize

Do this procedure for all blocks \rightarrow Then combine

$$\begin{cases} n_A = 5 \\ n_B = 5 \end{cases}$$

block size \rightarrow

30 patients divided into 3 blocks

what if I want only 2 blocks

?	1	!	16	1	30 \rightarrow 1
	2				

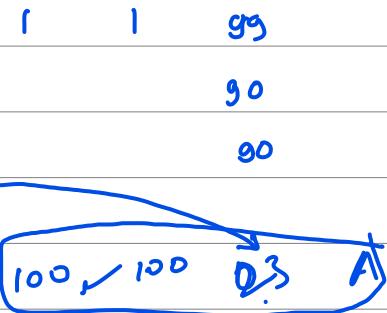
$n_A = 15$
 $n_B = 15$

$8-A$
 $T-B$

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

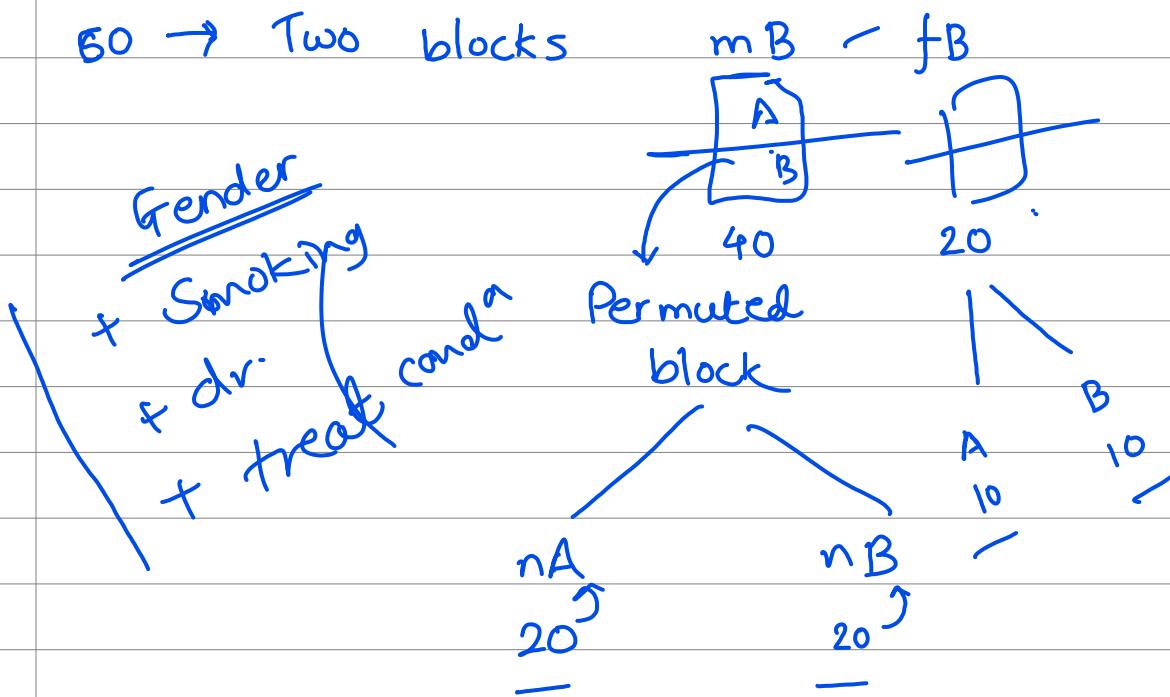
Adaptive Randomizations

① Treatment Adaptive Randomization

② Covariate A R

(Stratified Randomization)

③ Response A R



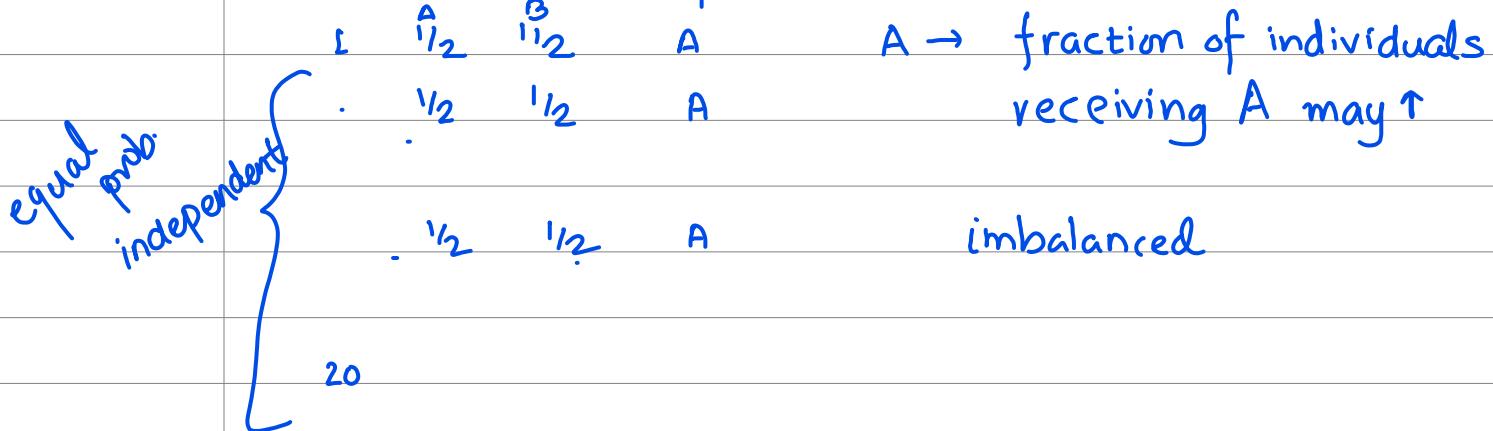
* Covariate :- Strata \rightarrow Covariate - Seq's -

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

Covariate - Groups - ✓ Permutated

Complete - Randomiz. 4 - NM

* Treatment Adaptive Randomization



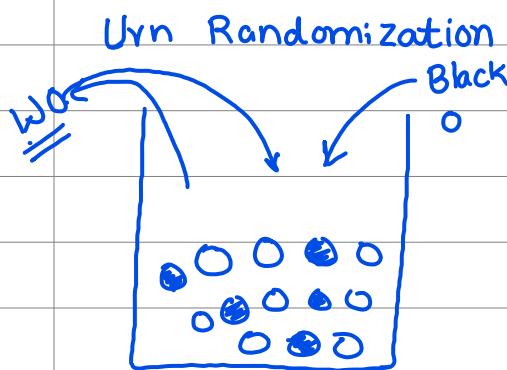
Efron (1971)

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')

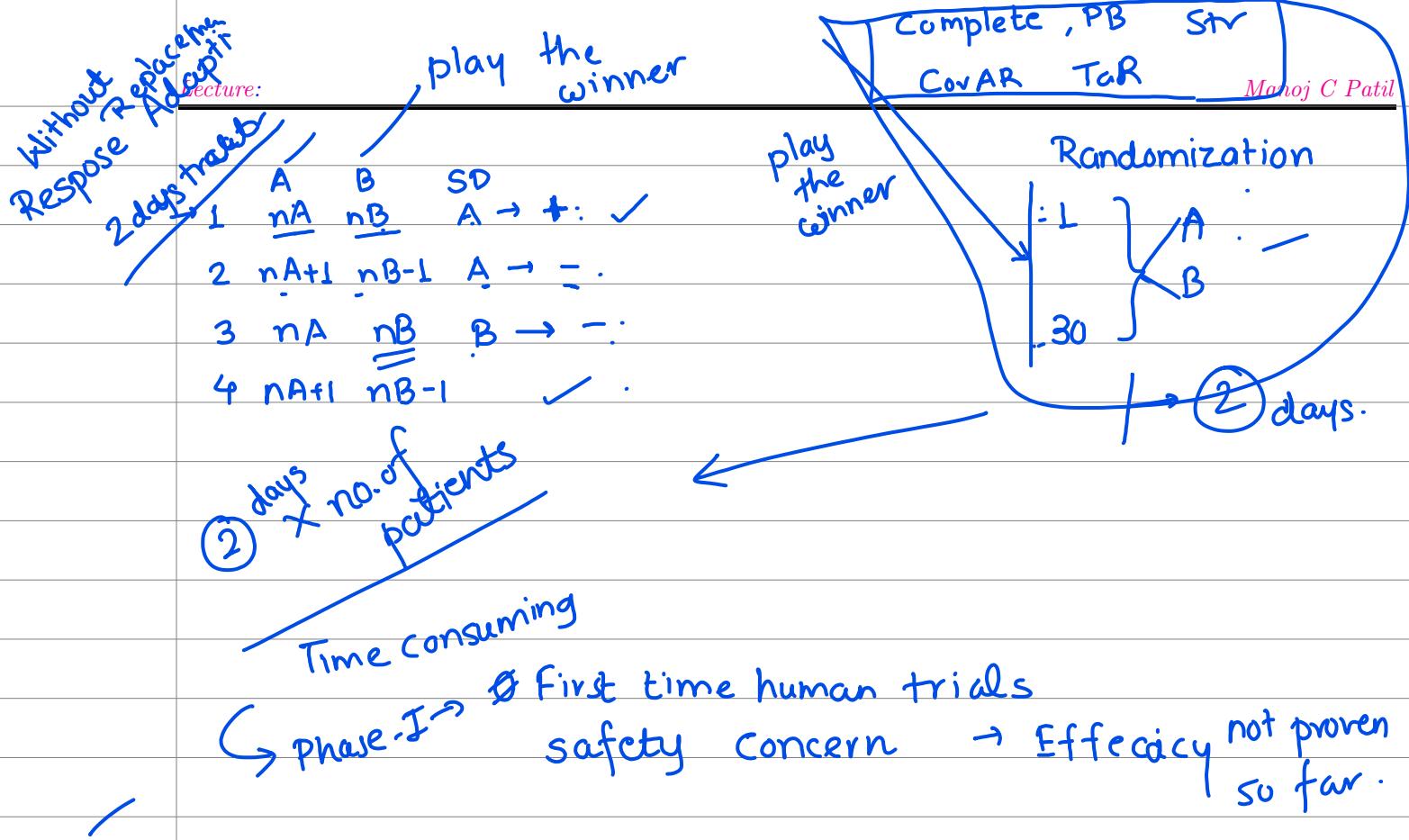
tre[1] =

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

```

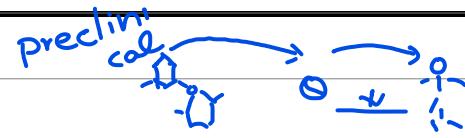
for (i=2:30){
  if(tre[i-1] == 'T') {nB=nB+1} else {nW=nW+1}
  tre[i] = Samp
}
  
```

* Response Adaptive Randomization
(Play the winner -)



$$\begin{array}{ll} n_A+1 & n_B-1 \\ n_A-1 & n_B+1 \end{array} \leftarrow \begin{array}{c} A+ / B- \\ A- / B+ \end{array}$$

Absent:- 2001, 2, 3, 4, 6, 9, 10, 12, 14, 16, 17, 23, 33, 34, 35, 43, 44, 45, 50, 51, 55 = 21 students
 Thank you.



Phases- clinical trials

I
mostly healthy
20-80 subjects

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

II
100-1000 subjects

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

II A
several hundreds subjects

extended phase II trials - Effectiveness

II B
several thousands

controlled & uncontrolled trials → Physicians Label

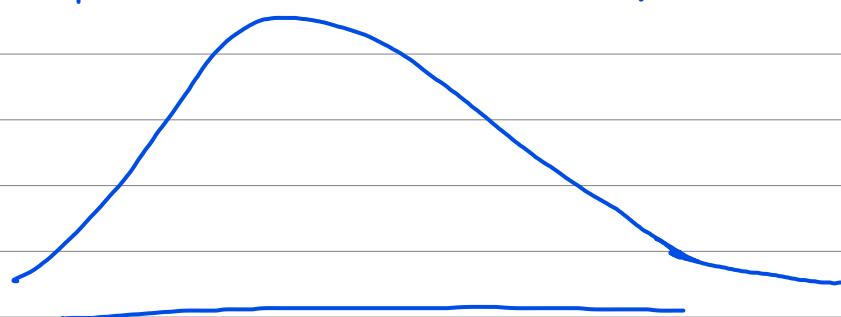
III
several thousands

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

IV
other
18-60 patients

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
therapeutic window

2 side
lower
1
same

MED Therapeutic window MTD

* Control ? ∵ Treatment

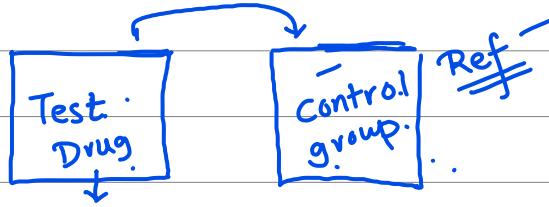
Ref: ① No treatment

② Placebo treatment

✓ ③ Active Drug

④ Dose-response concurrent

⑤ Historical concurrent



Drug is effective

(Therapeutic window) concurrent control

↑
Test

parac.

Rare disease :-

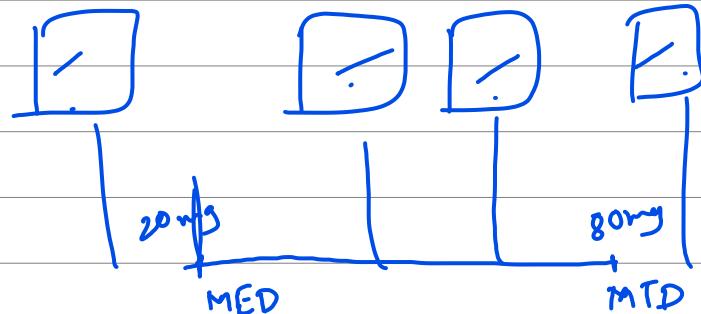
e.g. Brain tumor :-
10-12 patient



No. patient



1985
assume =



* Safety :-

Test

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

Phase-I ≈ 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

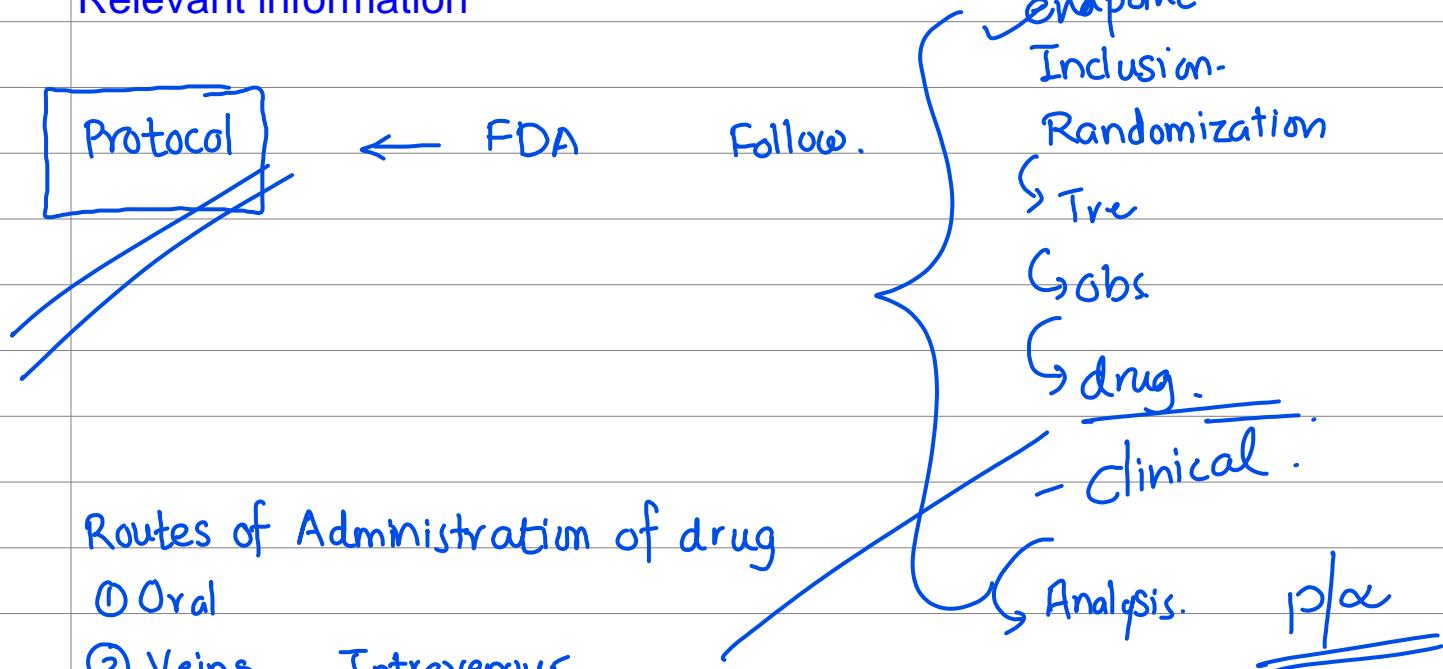
* Govt Health dept

* 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. ✓

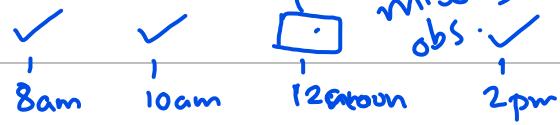
Ref

+ Milk ✓
 + Drug B ✓

① Dropouts ? Treatment →

who fails to complete

② missing value



③ Premature Termination.

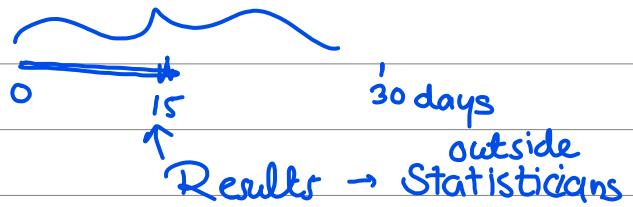


* Multicenter Trials :- ?

① No. of pat subjects ↑

② Results generalizable

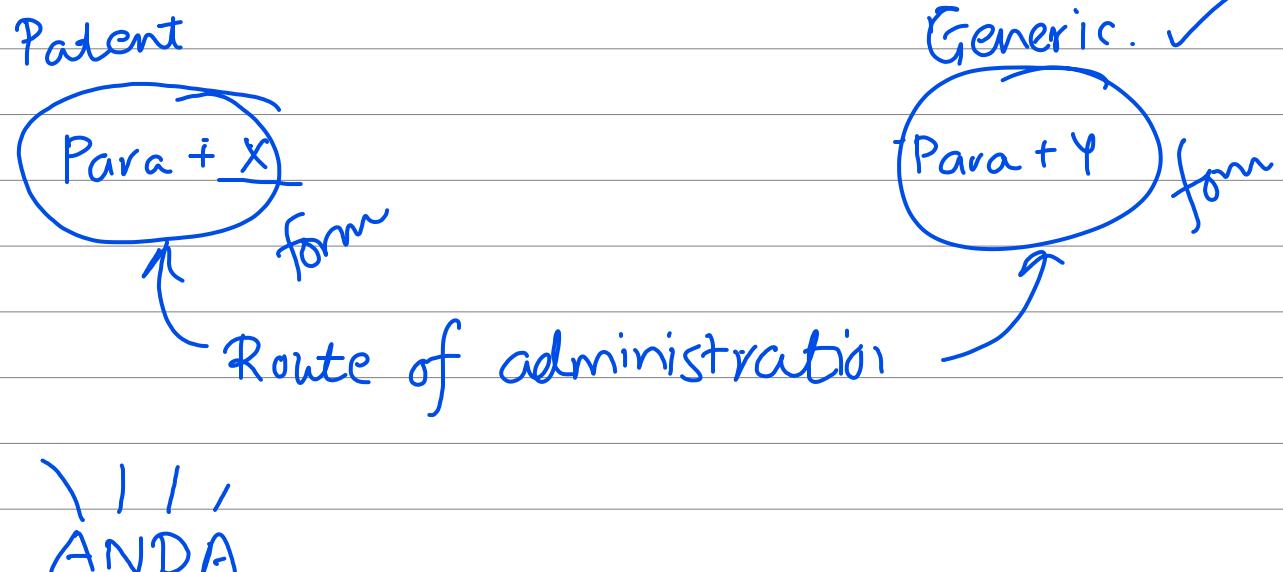
* Interim Analysis



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



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

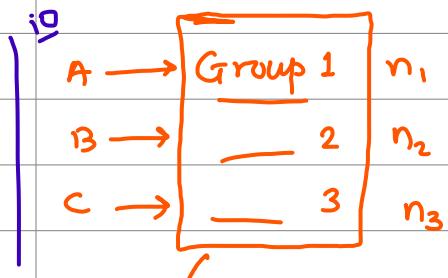
A.	<u>1, 4</u>	2
B.	2, 5, 8	3
C	3, 6, 7	3

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

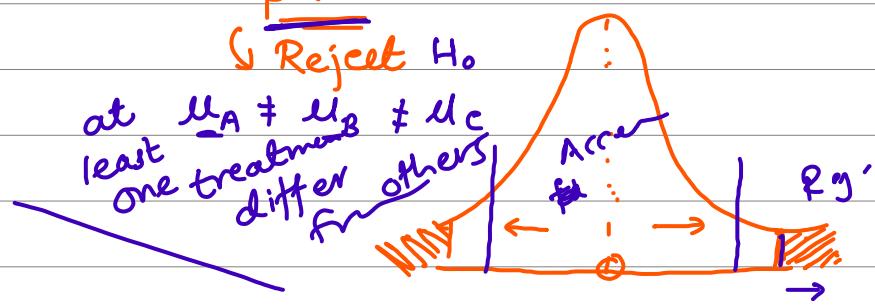
 F_{crit-2} $F_c < F_{table}$

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

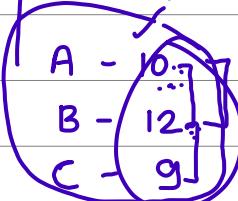
$$t = \frac{(\bar{x}_A - \bar{x}_B)}{\sqrt{MSE \left(\frac{1}{n_1} + \frac{1}{n_2} \right)}}$$

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

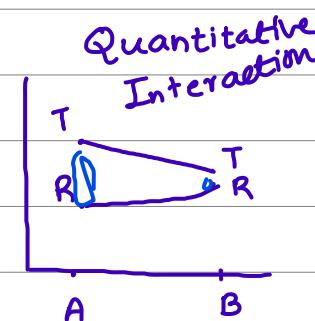
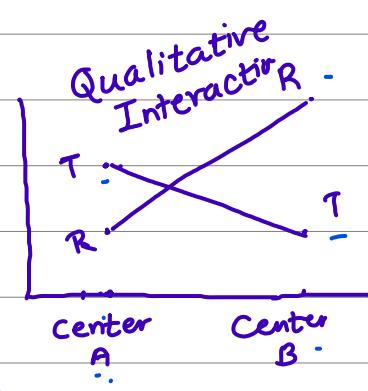
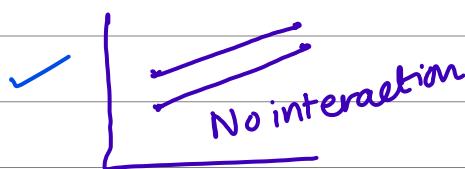
	Smoker	Non smoker
low	n_1	n_2
Moderate		
high		



r fobs per cell

③ General two way

Interaction Effect

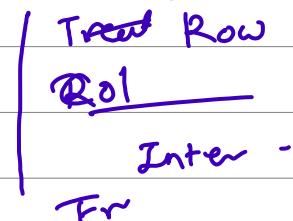


④ Factorial Designs? -

2^k factorial
↑ No of factors
levels.

	B_1	B_2	B_3
A_1	□	□	□
A_2	✓	✗	□
A_3			

Two-way with inter



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

sign

error $\rightarrow n-r.c$

MSF $\rightarrow \frac{n}{r.c}$

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

Interaction

effect identify

Confounding ?

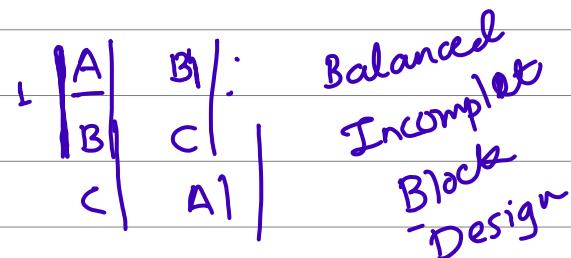
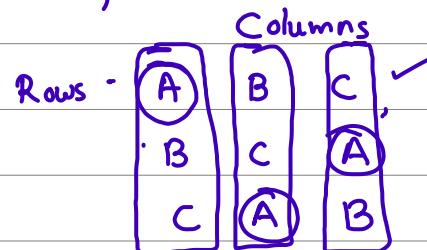
- due to some identified/unidentified factor effect

CRD RBD
1 2 3 Factorial

LSD

Latin Square Design

3 factors



Designs CT

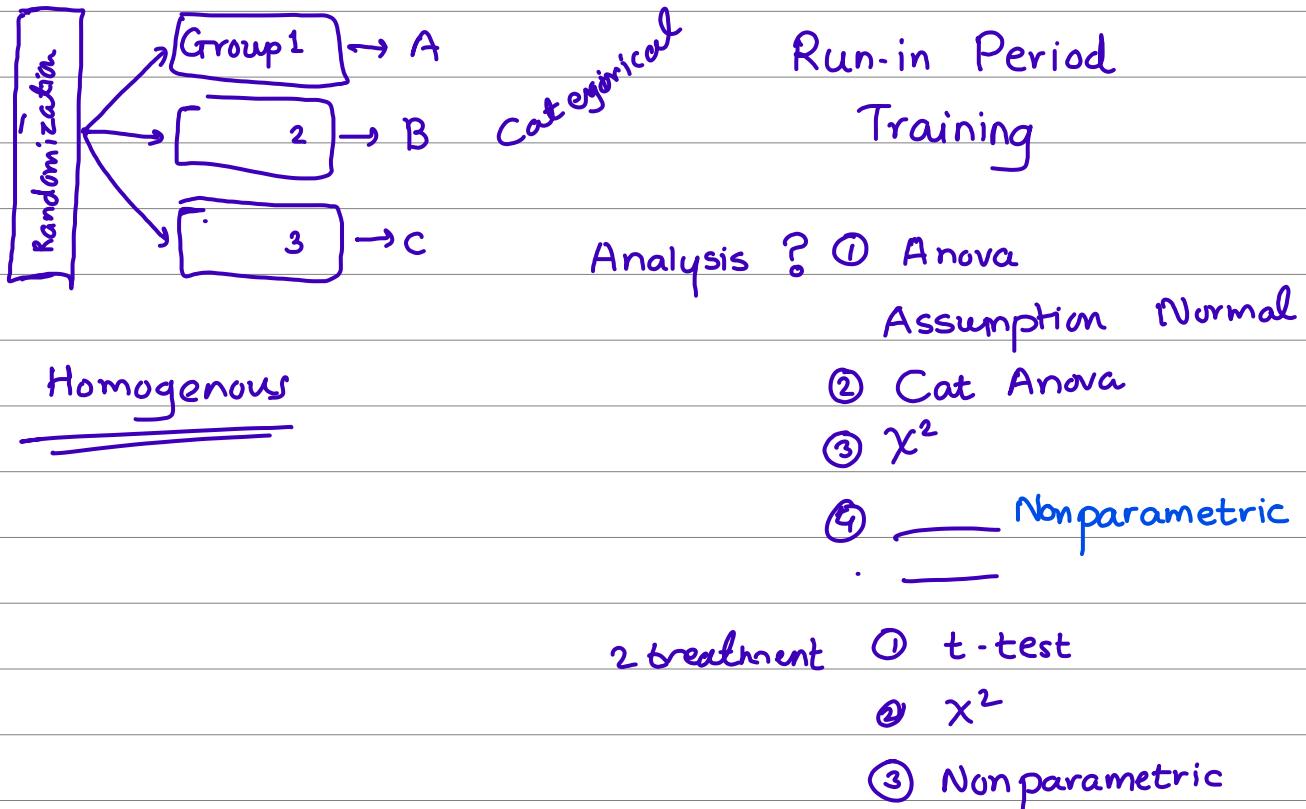
Obs: ① Test treat > better
Refere

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

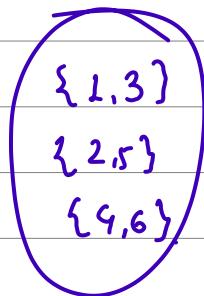
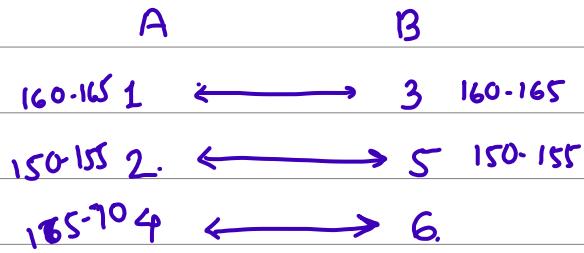
Control :-

Active Concurrent Controls

* Parallel Group Design 3 treatment A, B, C



Matched Pair



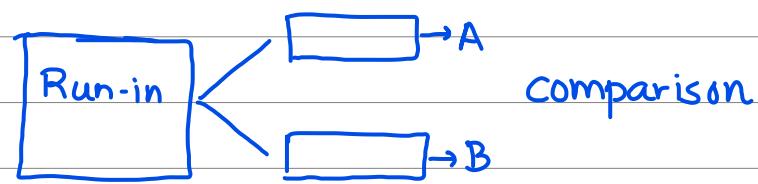
Abs : 4, 6, 9, 10, 13-14, 16, 22, . 30, 33-35, 39, 43-47, 50, 51, 53-55 = Total present 37

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

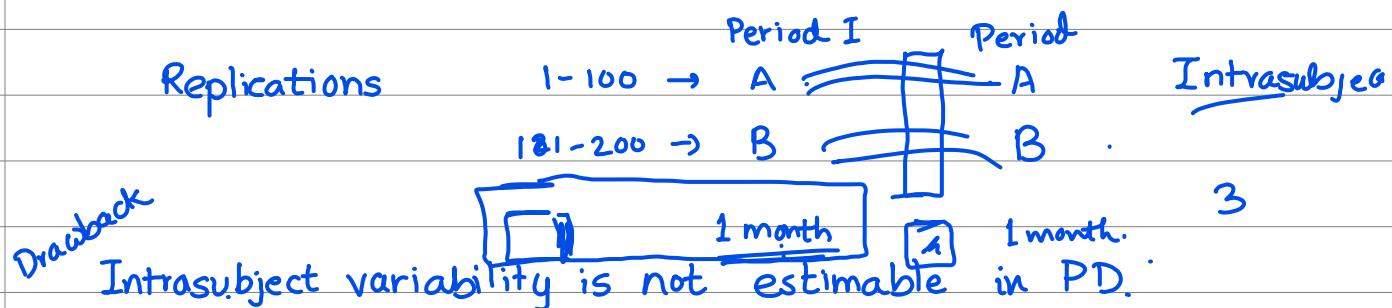
Variability \rightarrow Intersubject :- Same Single treatment \rightarrow diff sub \rightarrow diff responses variation.

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

log F

gg F

② FIR - baseline variable

↳ Covariate

↳ Inclusion Exclusion Criteria

baseline ✓

Clinical endpoint

③ Placebo respondent identify

④ Patient compliance

Nil by mouth

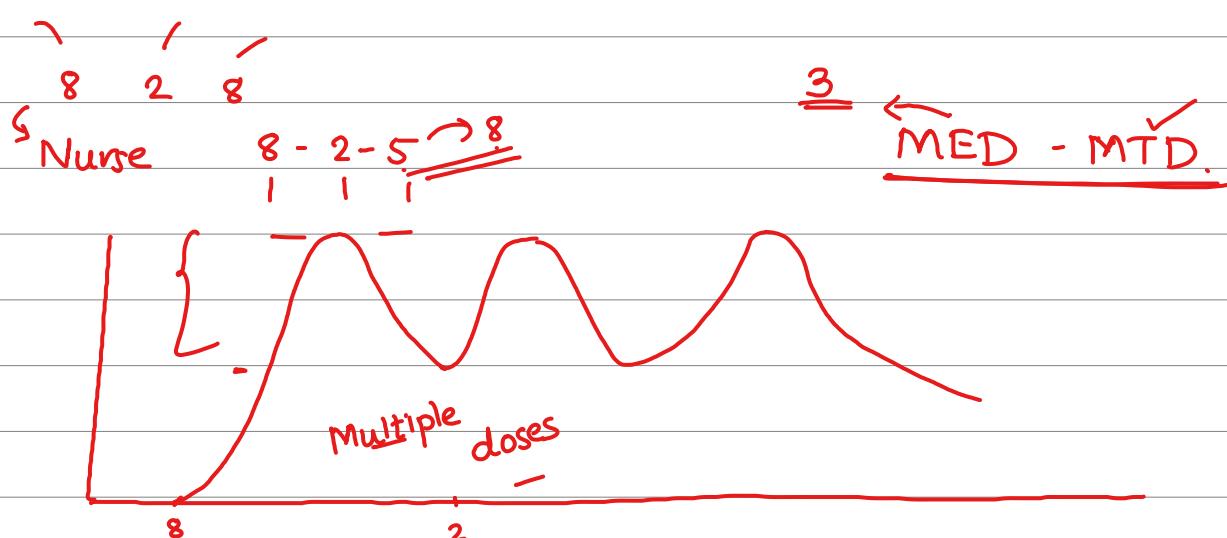
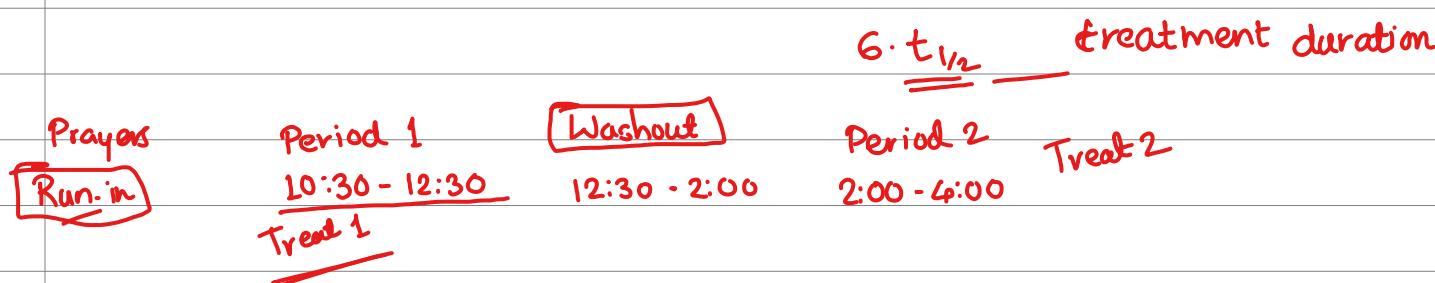
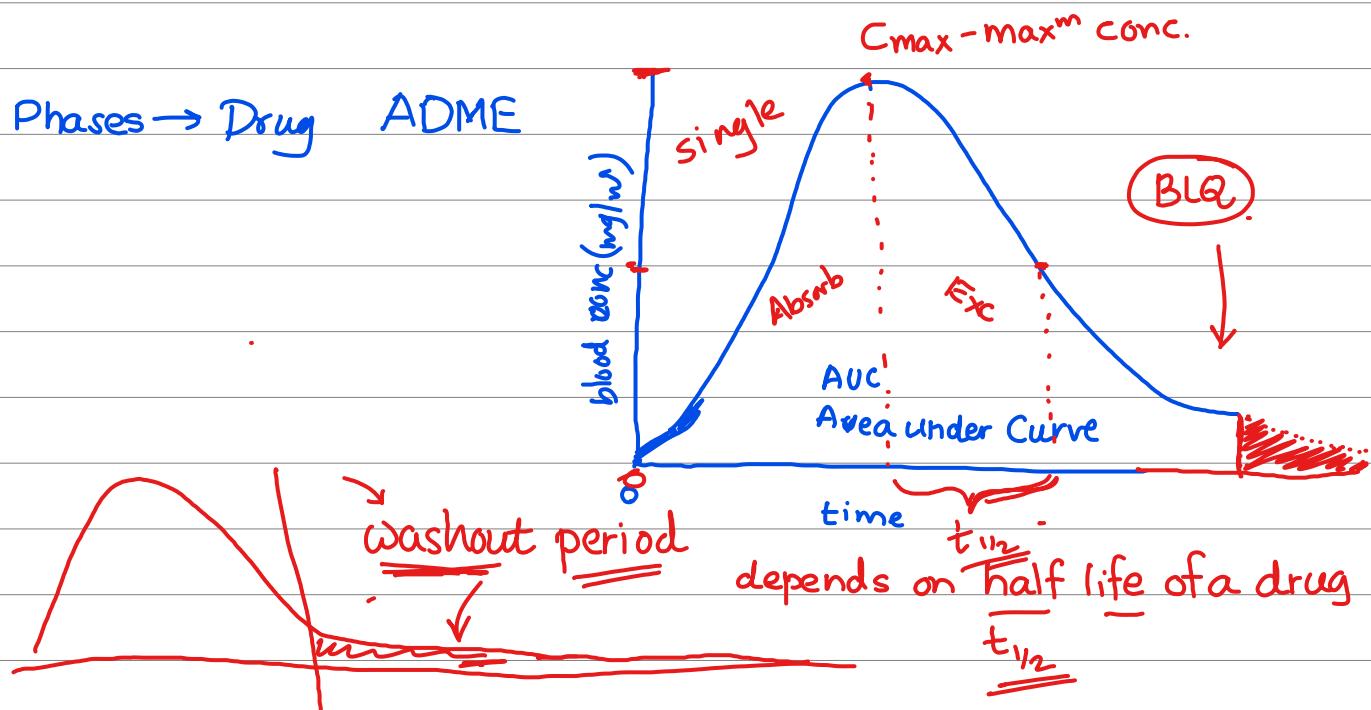


⑤ Washout period

for previous treat

② 8 10 12 2 4

8 10 12 2



Treatment Effect

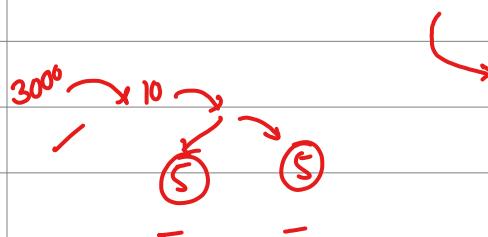
① Active ingredient] X I

② Placebo

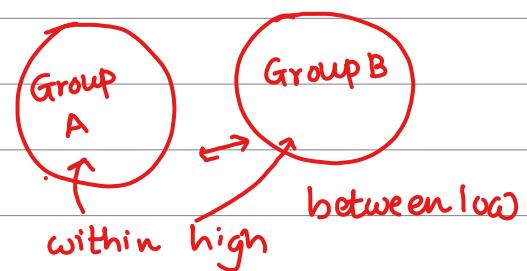
③ Disease] ✓

④ Other factor] ✓

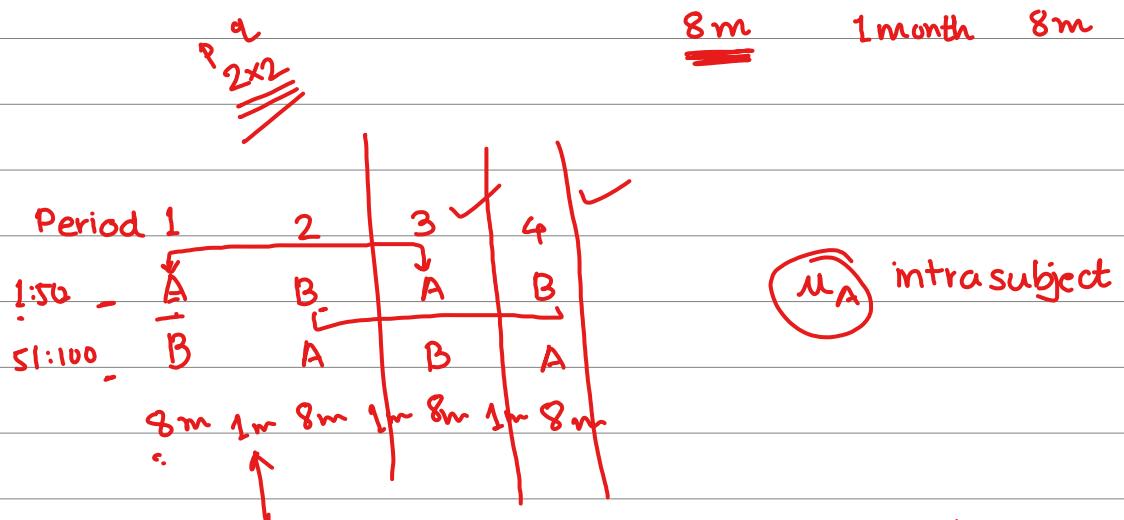
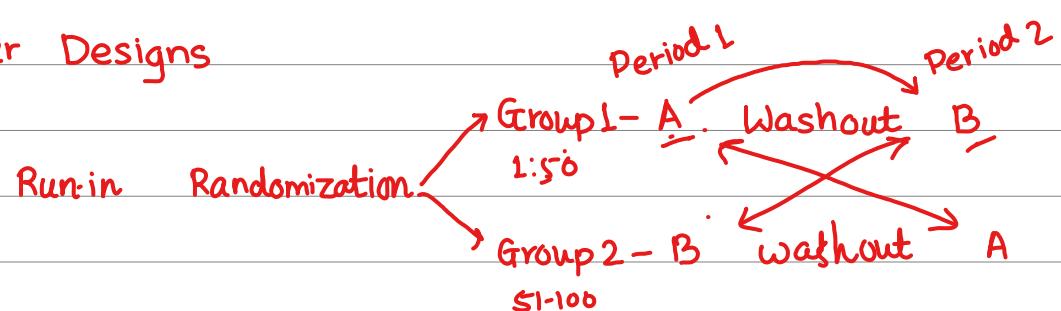
✓ Cluster Randomized design



ST-103
Cluster Sampling ?



Cross-over Designs



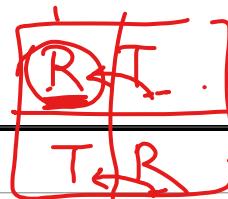
Complete Crossover

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	$f_R - F_T + C_T - C_R - F_T + F_R \Rightarrow 2(F_T + F_R) + (C_T - C_R)$		

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

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.

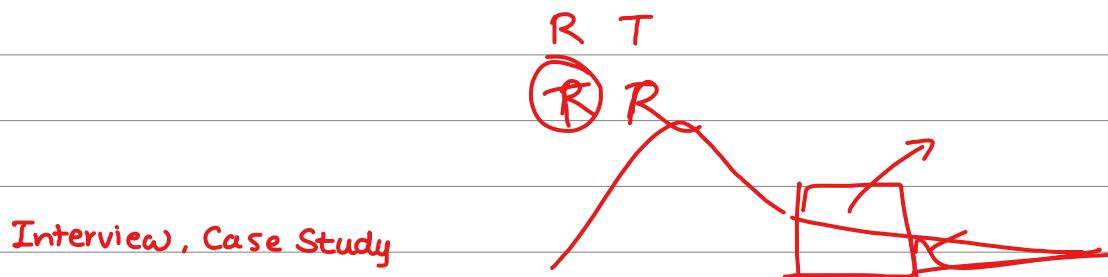
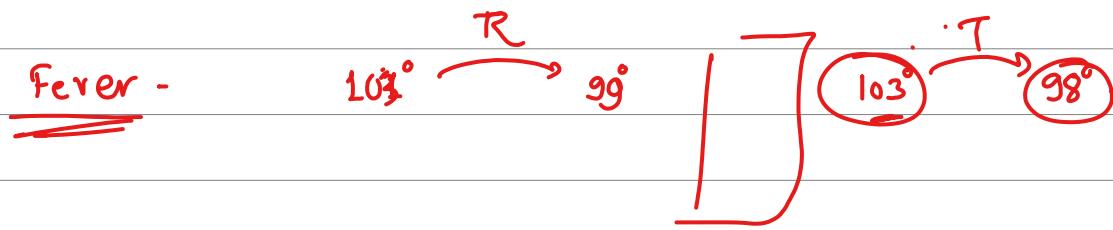
$$C_T - C_R = \text{Carryover effect} -$$

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

period seq
 $p \times q$

Cross-over design

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



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

	P1	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 $t=2$

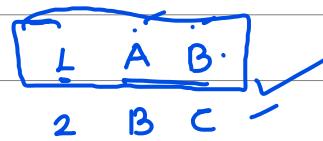
ei: $p>t$ or $q>t$

1	A	-	2	3	$q=3$
2	B	-	B	B	$p=2$
		-	A	A	2×3 $t \geq 2$

1	A	B	2	B	A
2	B	A	3	A	B
		-			3×2

Sik \rightsquigarrow

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

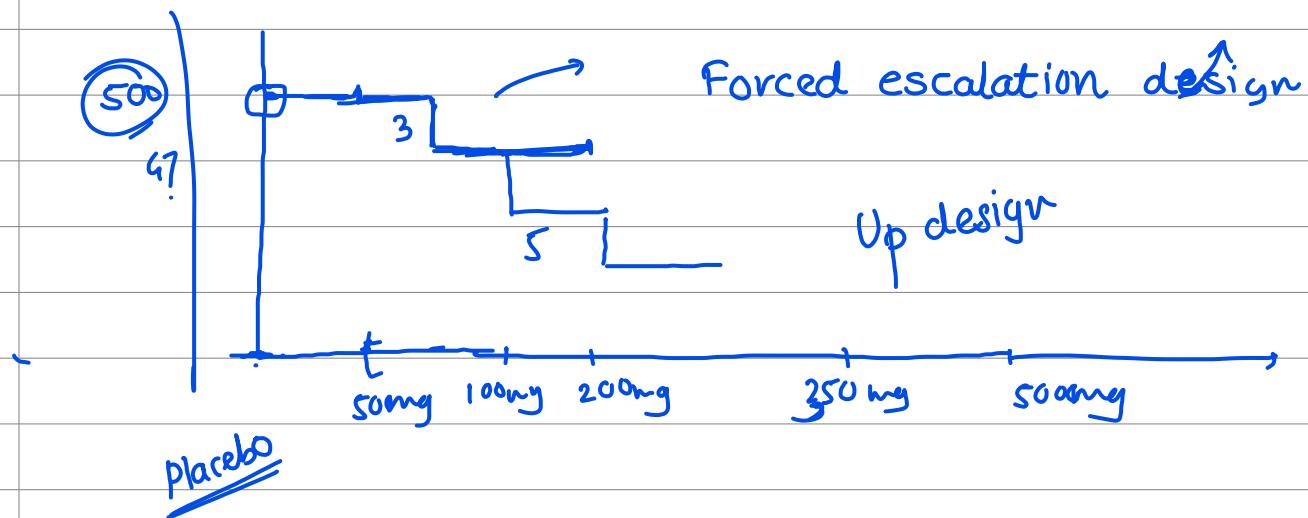
A BCD
B C DA
C DA B
D A B C

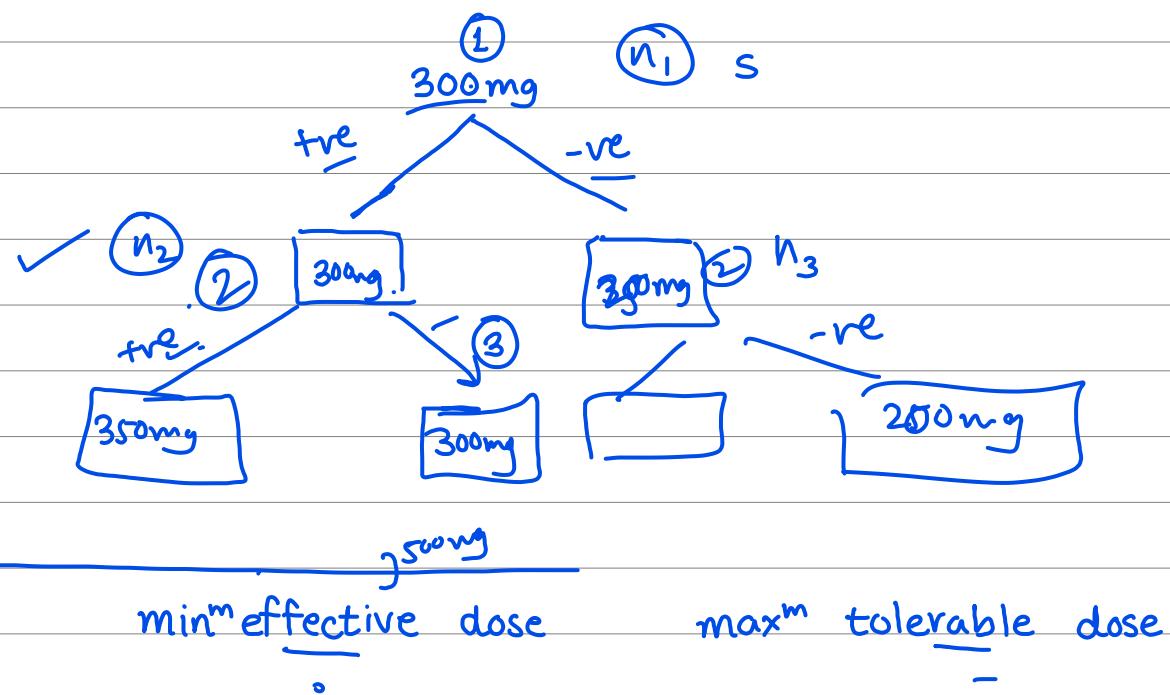
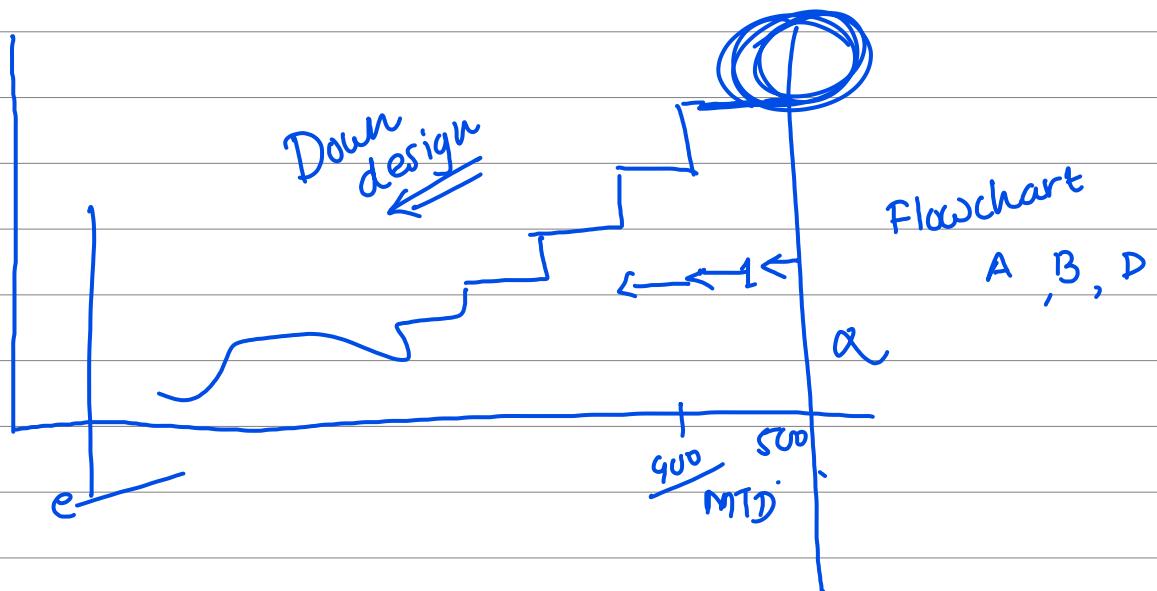
Titration Designs

Phase-I trials safety- evaluation

II

Titration. Therapeutic window [MED - MTD]





Dose- Response ~~Pre~~ Trials

① Parallel Dose Response

② Crossover

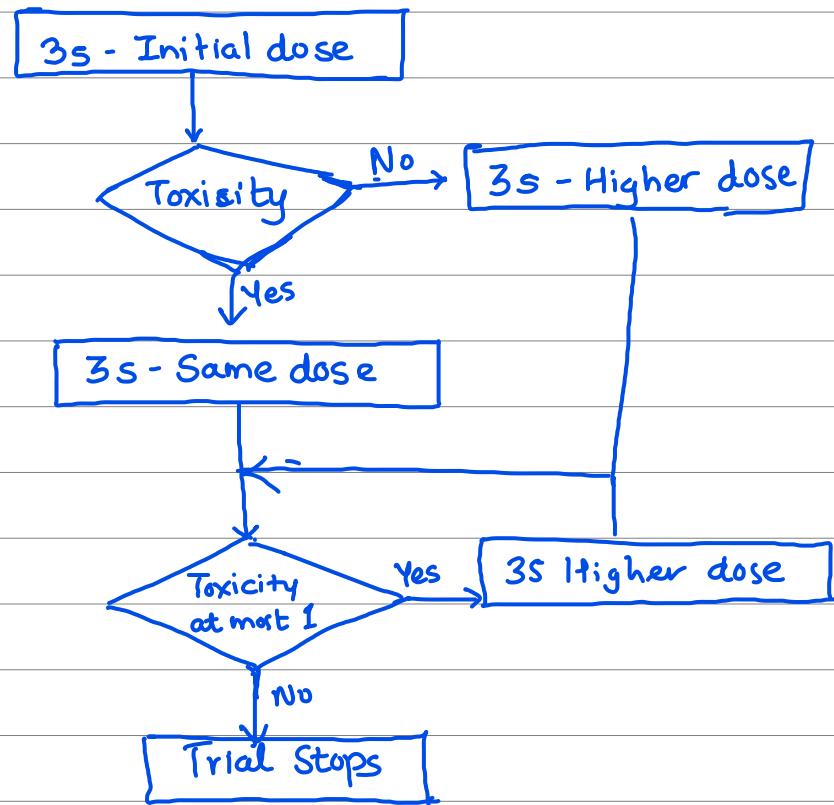
③ forced Titration

④ Optional Titration

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

Flowchart A Design A

Up ↑

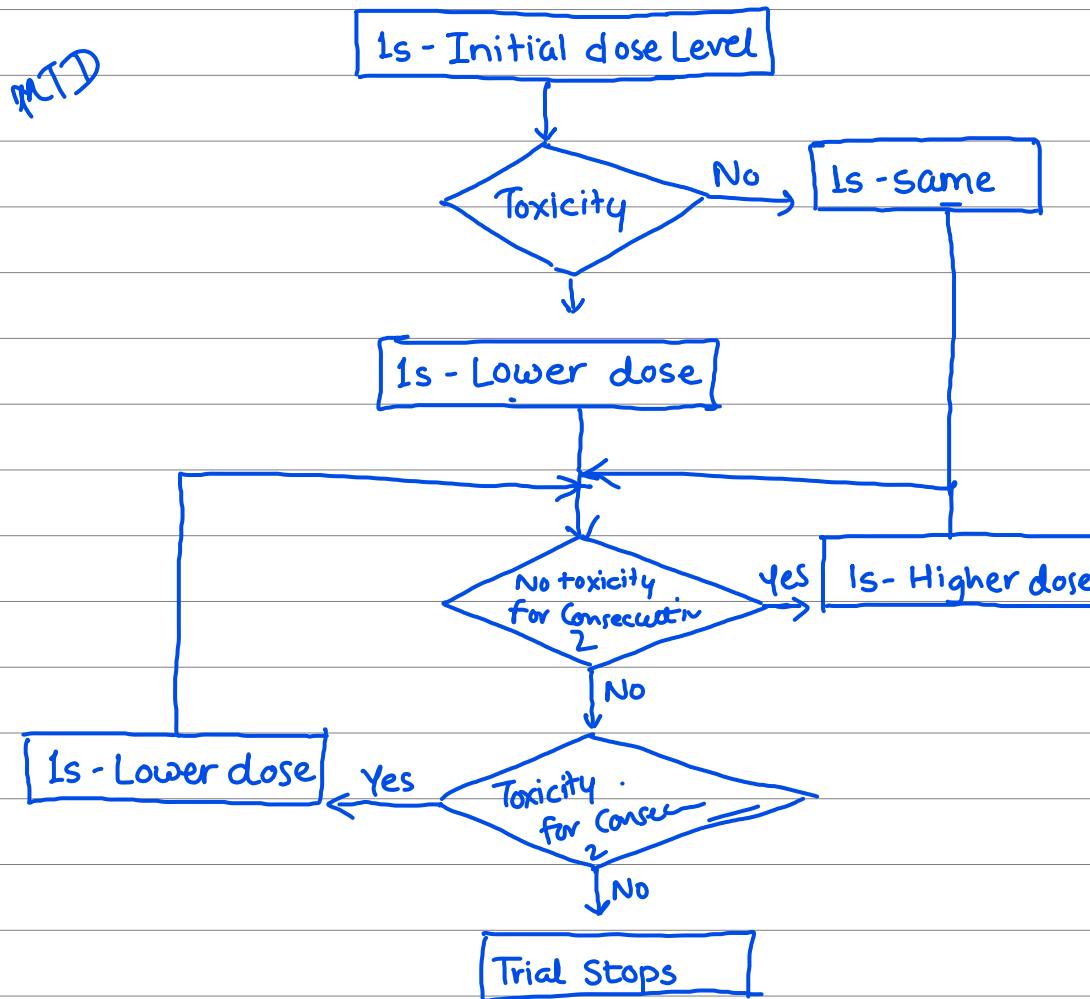


Flow

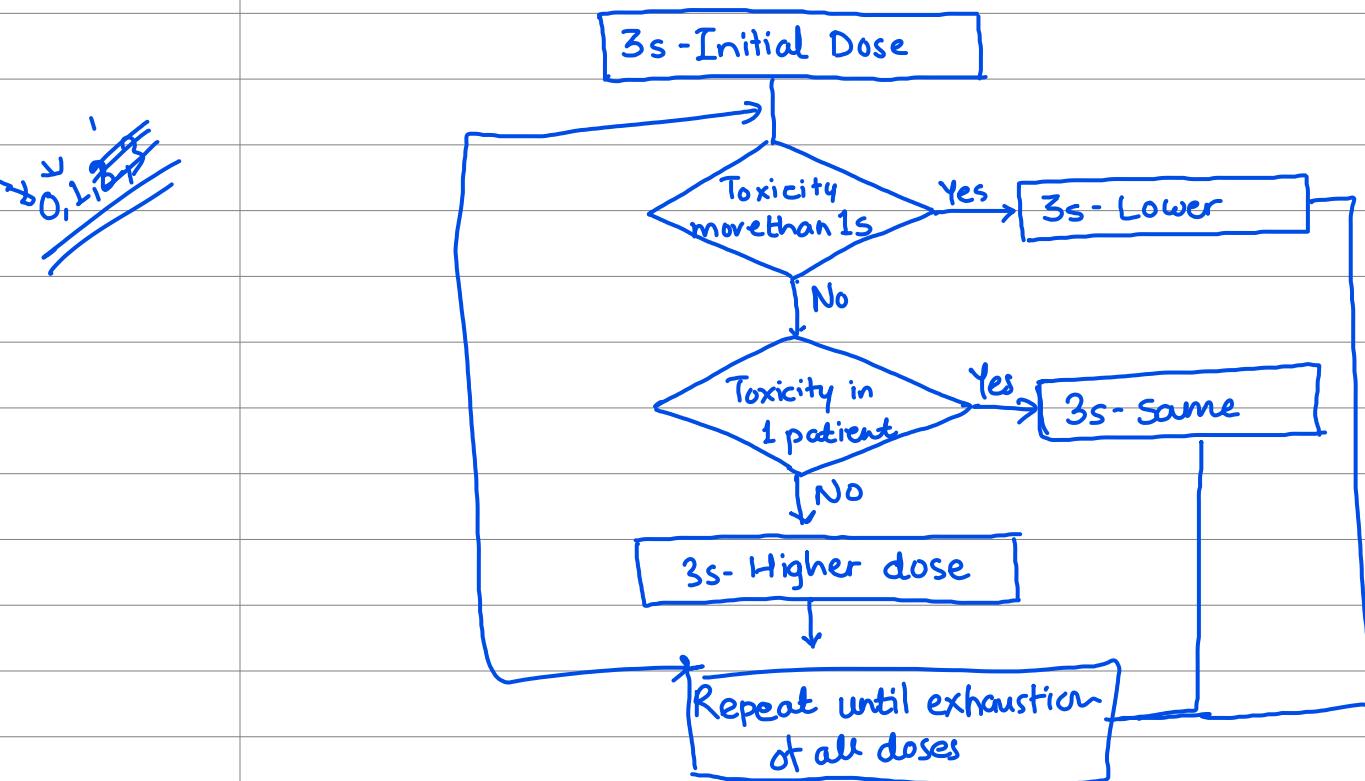
~~MED~~

Flowchart For Design B

down ↓



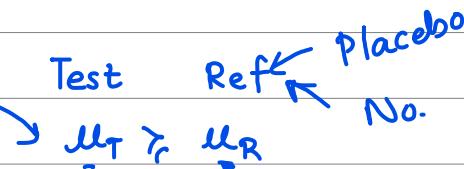
Flowchart for Design D :-



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.

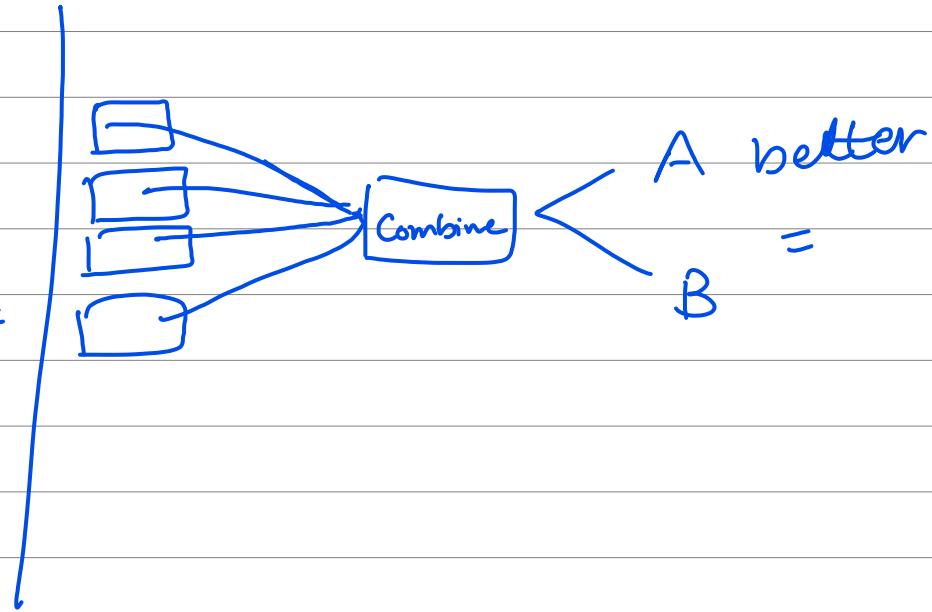
② Homogenous

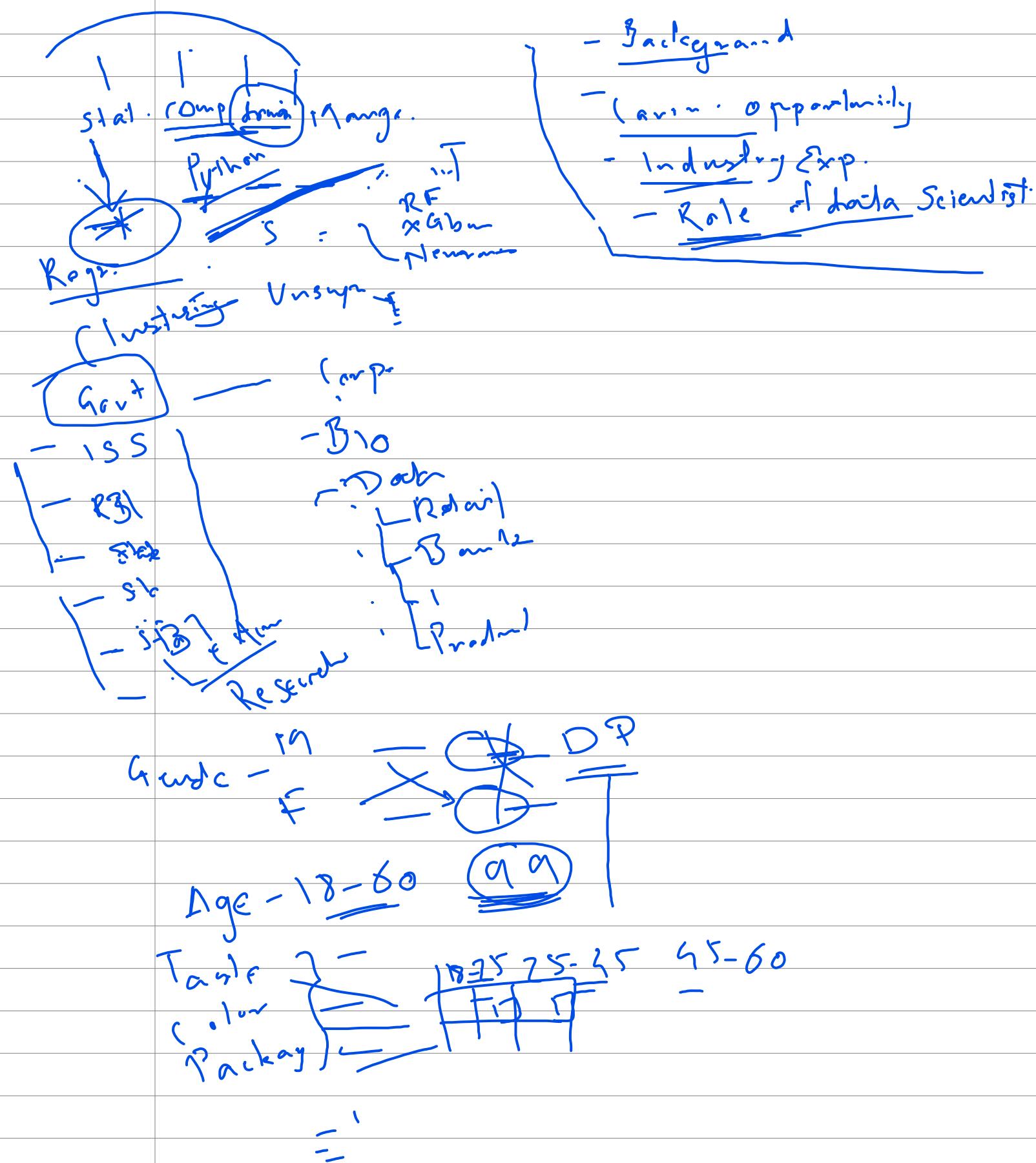
Multicenter:

Center Better

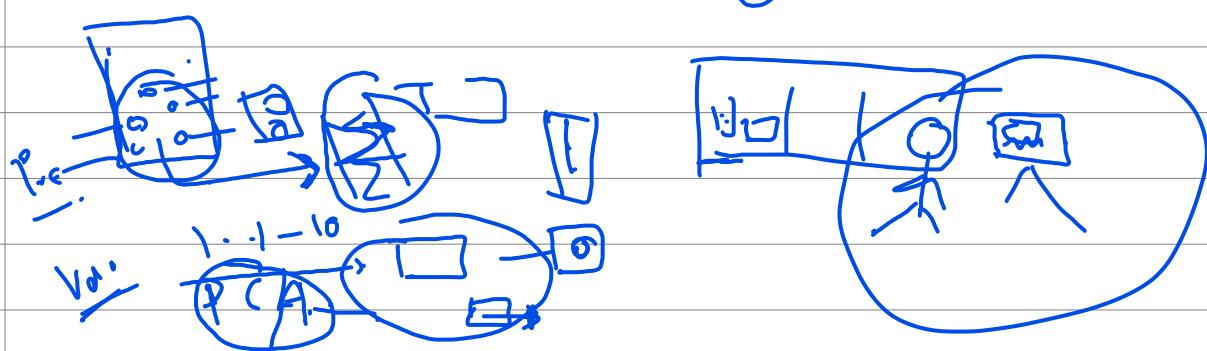
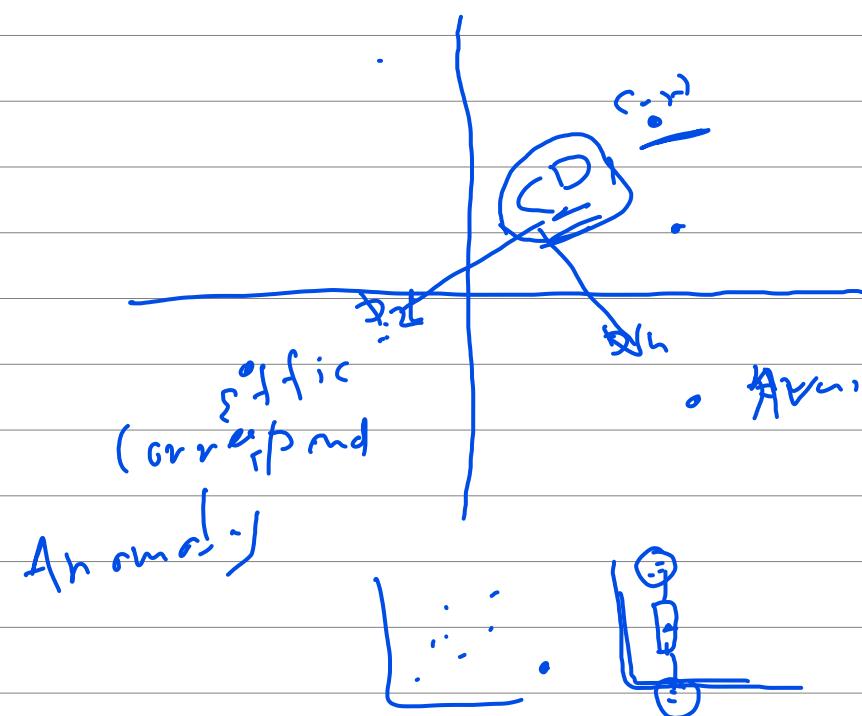
- 1 → A -
- 2 → A -
- 3 → B - 3/4
- 4 → A - =

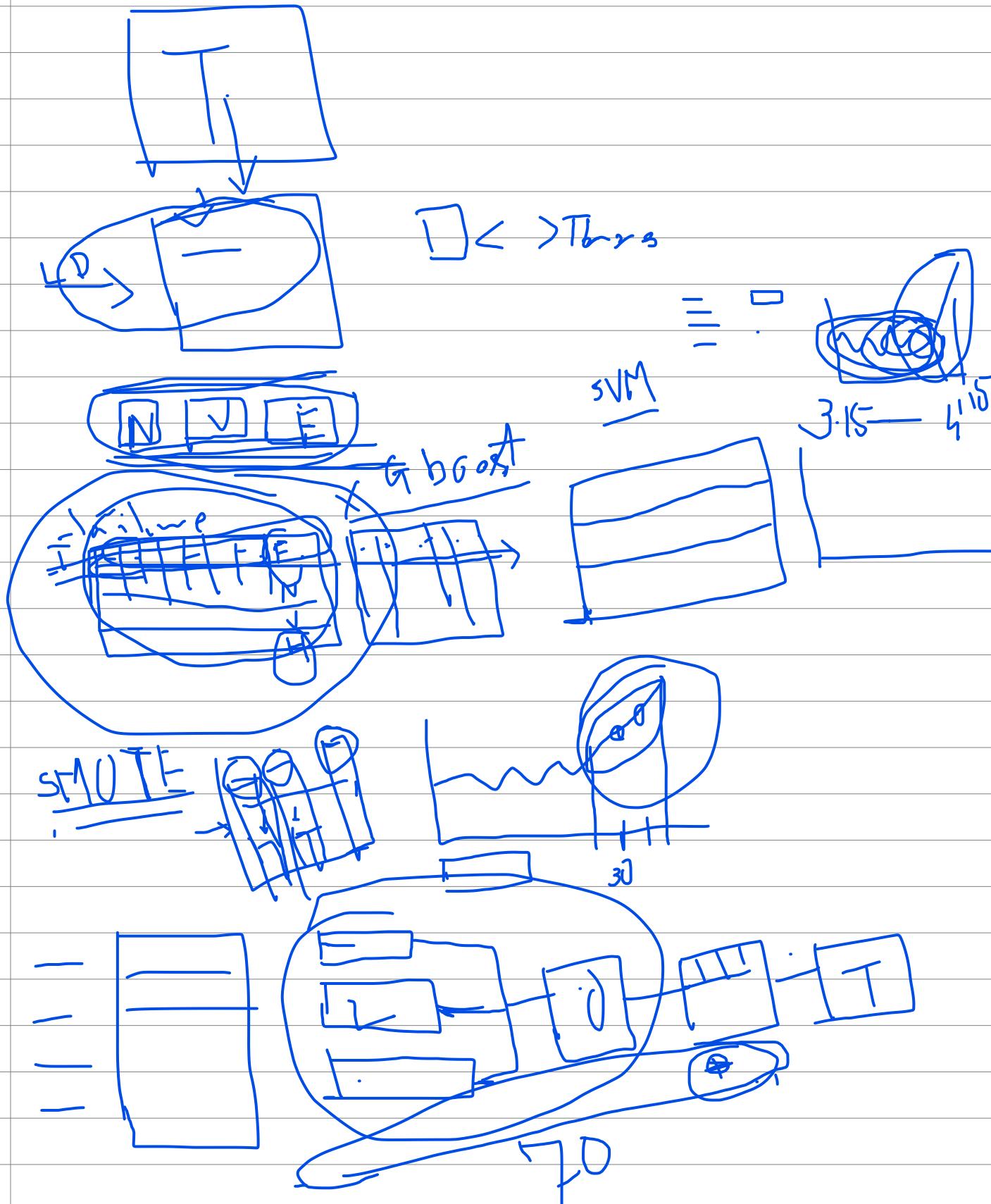
(A)

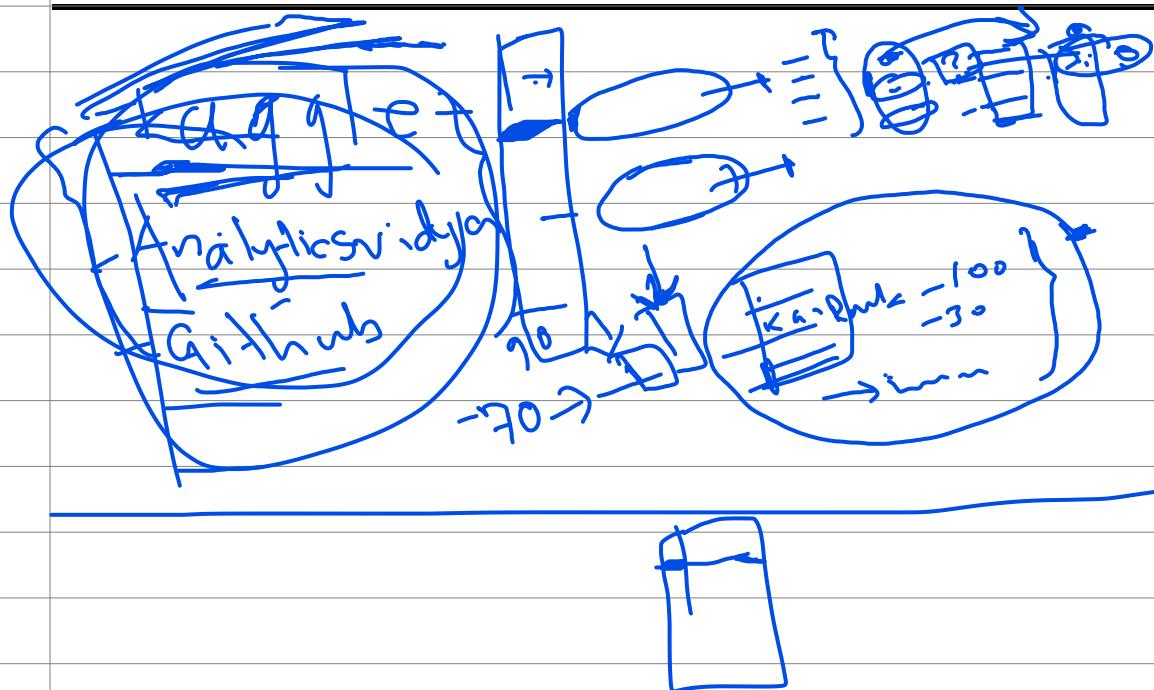




	cost	mail	fr.		
-CD	1	2	5	1-5	
-D1	3	5	5		
-D2					
-D3					
-D4					







d

E
-
-

Knowledge Transfer

* Repeated Measure

Age ✓	Treatment	at time of dosage			Gender ✓
		DBPO	DBPI	DBP2	
	A	Baseline		Y	
	B				

GLM

$$y_{ijk} = \mu + F_{AB} + G_{MF} + X\beta + \epsilon$$

GLM Regression

One way

$$\rightarrow y = \mu + \alpha_i + \epsilon_{ij}$$

Non full rank

individual parameter

$$y_i = \beta_0 + \beta_1 x_i + \epsilon_{ij}$$

full Rank

testi

$$Y = X\beta + \epsilon$$

ANOVA
Indicator variableRegression
Physical variable

② Random Effect model

$$y_{ij} = \mu + \underline{\alpha_i} + \varepsilon_{ij}$$

↓

$\sim N(\alpha, \delta_2^2)$

$\varepsilon_{ij} \sim N(0, \sigma^2)$

Fixed Effect

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

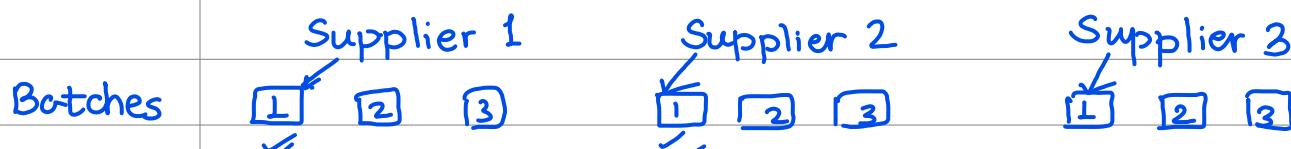
$$\epsilon_{ij} \sim N(0, \sigma^2)$$

③ Two way model

Column

	Block 1	Block 2	Block 3
Row	Treat A	.	.
	Treat B	.	.

Nested Design



Obs.

y_{111}

y_{112}

y₁₁₃

• Batches nested under suppliers.

y₃₁₁

312

93

4

Not equivalent
why?

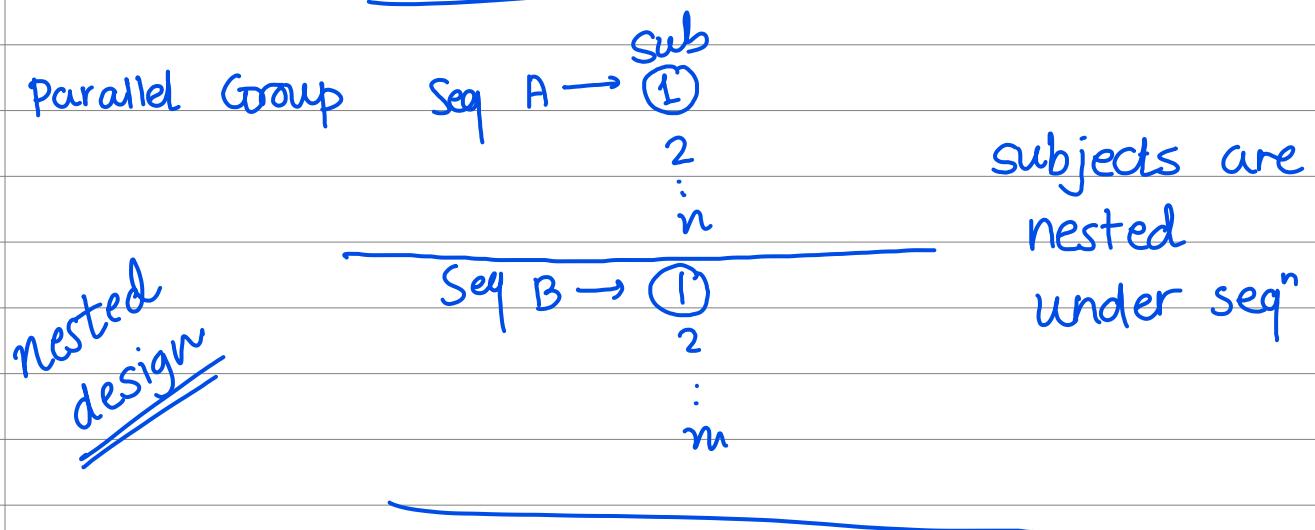
Blocks / Batches

Not equivalent

Supplier 1

	1	2	3
1	3	3	3
2	3	3	
3	3	3	

τ -obs / cell two way
setup

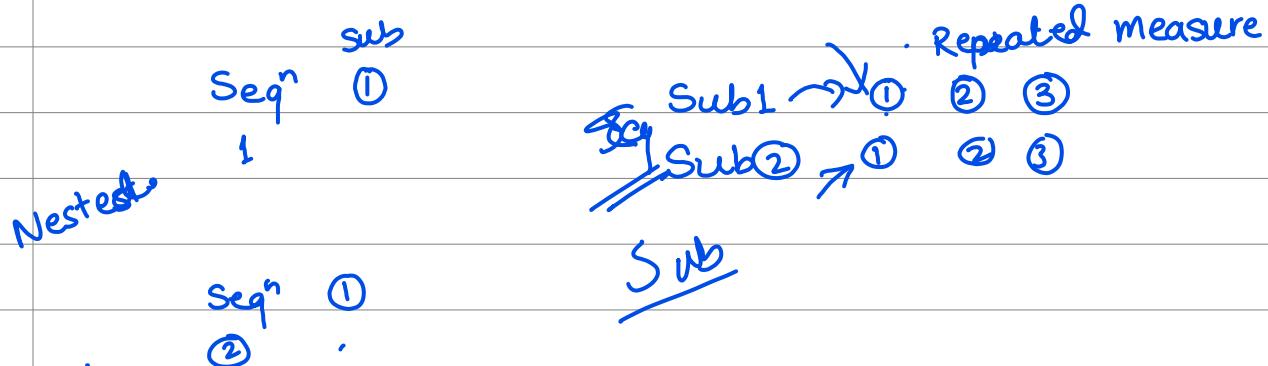


Minitab :-

$$\begin{array}{ccccccc}
 Y_{ij} & \xleftarrow{\text{Sub}} & \xleftarrow{\text{Seq}^n} & \text{Peri} & \text{Drug} & + & \mu + \\
 1 & 1 & . & . & . & . & \\
 2 & 2 & . & . & . & . & \\
 3 & 1 & . & . & . & . & \\
 \vdots & & . & . & . & . & \\
 \hline
 \end{array}$$

nested

~~SAS~~ ✓ model $- Y = \underline{\text{Drug}} \quad \underline{\text{Seq}^n} \quad \underline{\text{Period}} \quad \underline{\text{Sub}}(\underline{\text{Seq}^n}) + \text{carry}$

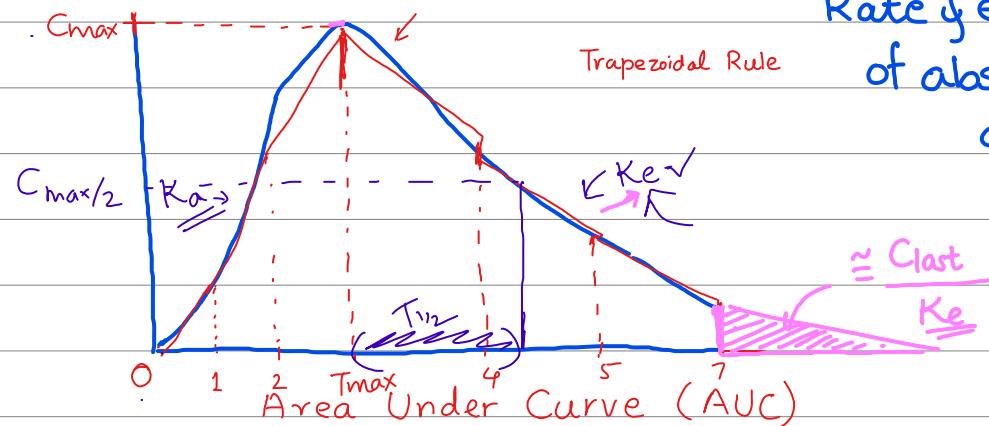


Abs : 2, 9-12, 14, 16-17, 22, 33-35, 38-39, 43-45, 47, 50

53, 56.

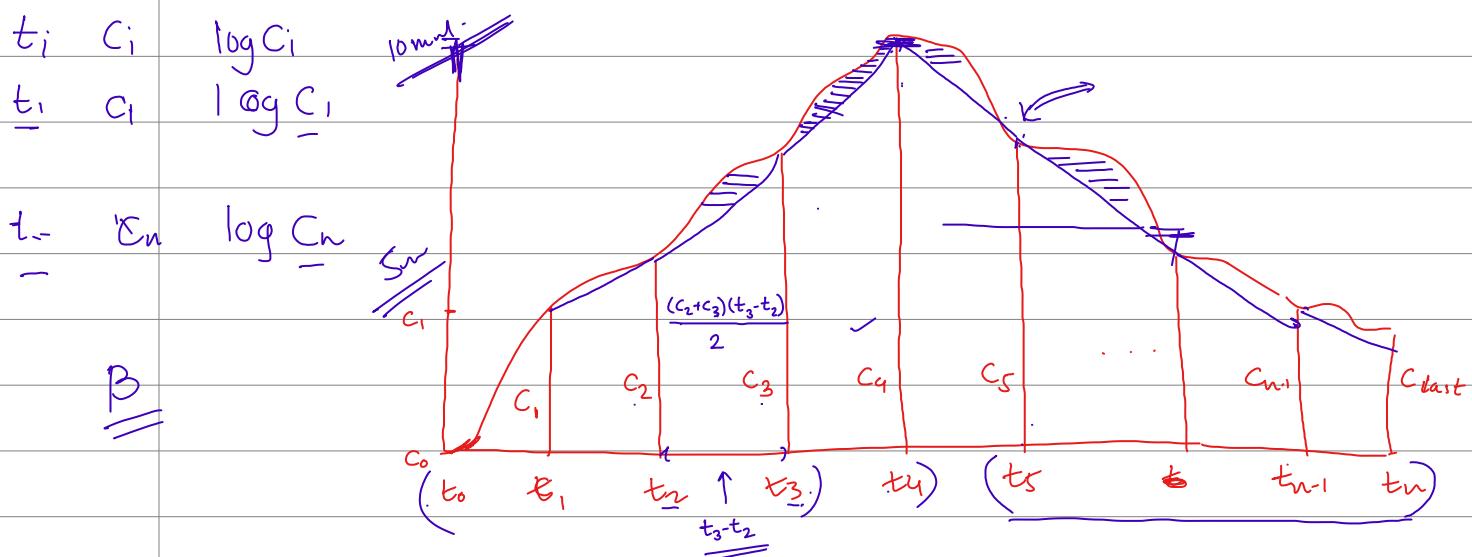
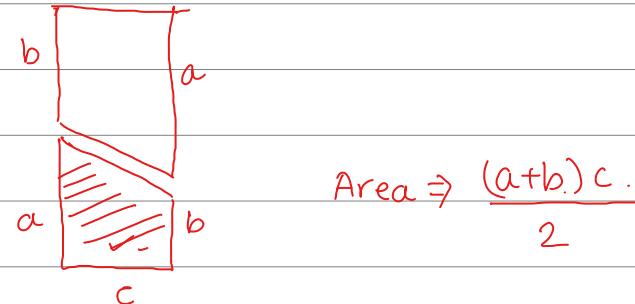
Pharmacokinetics Parameters

ADME
 conc. blood, urine,
 Rate & extent
 of absorption
 drug



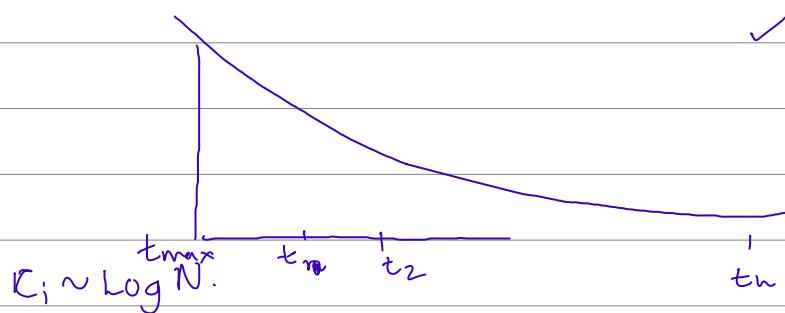
✓ $C_{\text{max}} = \text{max}^m \text{ conc of drug in blood}$

✓ $T_{\text{max}} = \text{Time at which max}^m \text{ conc. is achieved.}$



✓ $AUC_{(0-t)} = \sum_{i=1}^n \frac{(c_i + c_{i-1})(t_i - t_{i-1})}{2}$

$A_{(t-\infty)} = \frac{C_{\text{last}}}{K_e}$, $AUC_{(0-\infty)} = AUC_{(0-t)} + AUC_{(t-\infty)}$



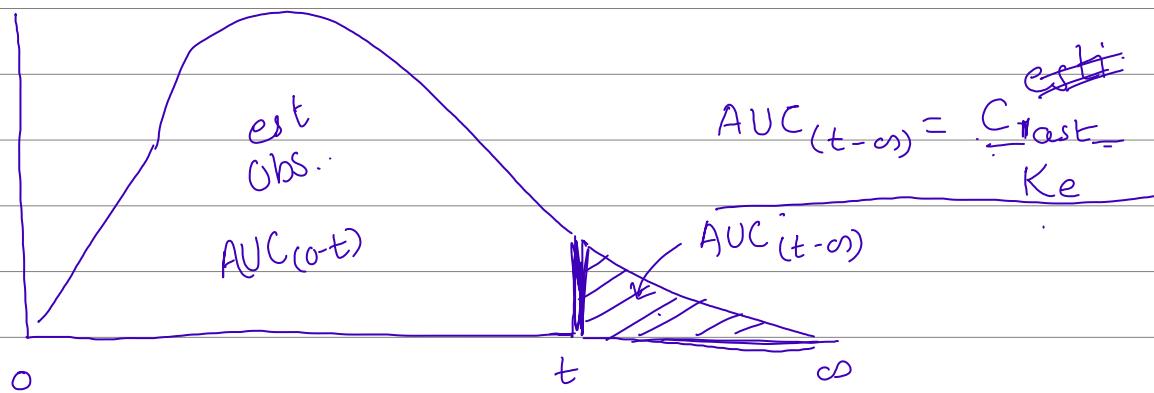
$$\underline{\log C_i} = \alpha + \beta t_i + \epsilon_i$$

$$K_e = -2.303 \alpha / \beta$$

$t_{1/2} \Rightarrow$ half life of a drug

Time taken by the drug to be half of C_{max}

$$-t_{1/2} \cong \frac{0.693}{K_e} \rightarrow \text{Treatment Duration} \Rightarrow 6 \cdot t_{1/2}$$



$$AUC_{(0-\infty)} = AUC_{(0-t)} + AUC_{(t-\infty)}$$

$$= \sum_{i=1}^n \frac{(C_i + C_{i-1})(t_i - t_{i-1})}{2} + \frac{C_{last}}{K_e}$$

Abs :- 6, 10, 15, 17, 23, 34.35, 43-45, 47, 50, 55

Abs :- 6, 10, 17, 23, 27, 35, 37, 39, 43-45, 47, 50, 54

$$\begin{array}{c}
 \cancel{Y_{ik}} \\
 \begin{array}{cc|c|c|c}
 & & U_{ik} & D_{ik} & O_{ik} \\
 \boxed{Y_{11}} & \boxed{Y_{21}} & Y_{11} + Y_{21} & \frac{(Y_{21} - Y_{11})}{2} & D_1 \\
 \vdots & & \checkmark & \checkmark & \\
 \boxed{Y_{12}} & \boxed{Y_{22}} & Y_{12} + Y_{22} & \frac{(Y_{22} - Y_{12})}{2} & -D_2
 \end{array}
 \end{array}$$

$$\delta_u^2 = \frac{(n_1-1) \delta_{u_1}^2 + (n_2-1) \delta_{u_2}^2}{n_1+n_2-2} \quad \delta_d^2 = \frac{(n_1-1) \delta_{d_1}^2 + (n_2-1) \delta_{d_2}^2}{\sqrt{n_1+n_2-2}}$$

$$\begin{array}{c}
 \hat{C} = \bar{U}_2 - \bar{U}_1 \\
 \sqrt{(\hat{C})} = \hat{\delta}_u^2 \left(\frac{1}{n_1} + \frac{1}{n_2} \right) \\
 \hat{F} = \bar{D}_2 - \bar{D}_1 \\
 \sqrt{(\hat{F})} = \hat{\delta}_d^2 \left(\frac{1}{n_1} + \frac{1}{n_2} \right) \\
 \hat{P} = \bar{O}_2 - \bar{O}_1 \\
 \sqrt{(\hat{P})} = \sqrt{(\hat{F})}
 \end{array}$$

$$\begin{array}{l}
 U_1 = \underline{Y_{11}} + Y_{21} \\
 V(U_1) = V(\cancel{2S_{in}} + \epsilon_{i11} + \epsilon_{i21}) \\
 = 4\delta_s^2 + 2\delta_e^2
 \end{array}$$

$$\left\{ \begin{array}{l} D_1 = \frac{\gamma_{21} - \gamma_{11}}{2} \\ \sqrt{D_1} = \sqrt{\frac{(\varepsilon_{i21} - \varepsilon_{i11})}{4}} \\ = \frac{2\delta_e^2}{4} = \frac{\delta_e^2}{2} \end{array} \right.$$

$$t_{\text{stat}} = \frac{\hat{F}}{\sqrt{V(\hat{F})}}$$

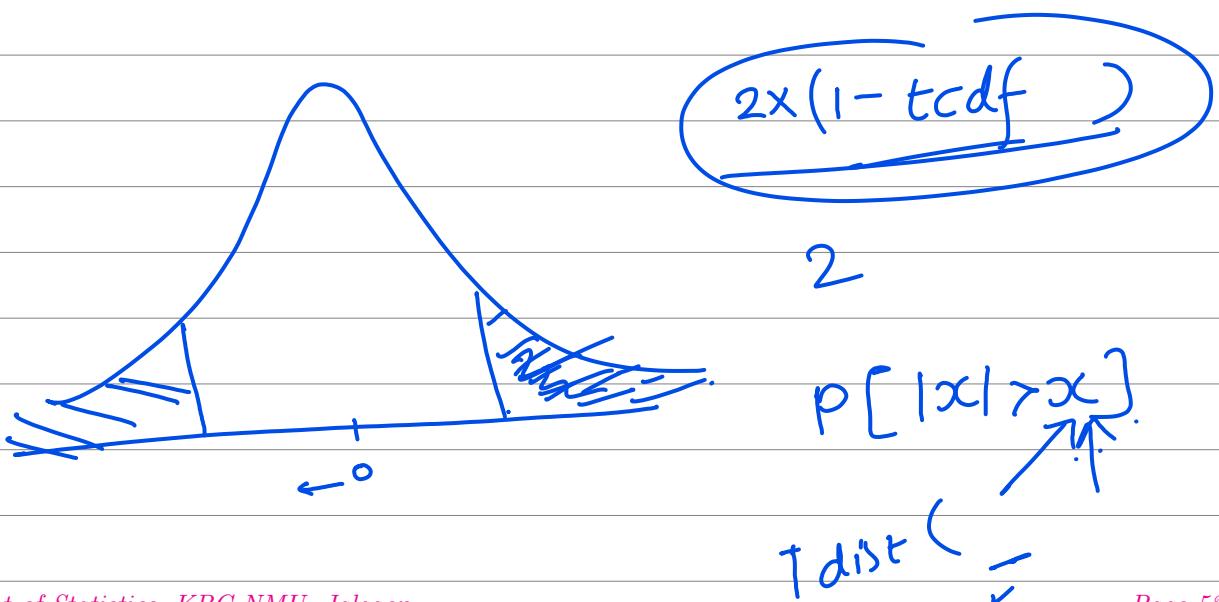
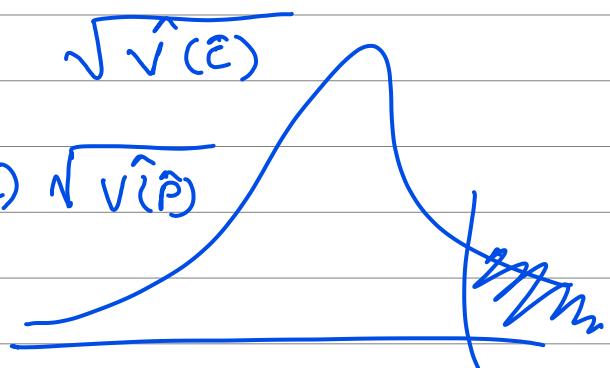
Direct drug

$$\hat{F} \pm t(\alpha/2, n_1+n_2-2) \sqrt{V(\hat{F})} =$$

Carry over

$$\hat{C} \pm$$

$$\hat{P} \pm t(\alpha/2, n_1+n_2-2) \sqrt{V(\hat{P})}$$



$$\begin{aligned}
 SStotal &= \sum_{K} \sum_{j} \sum_{i} (y_{ijk} - \bar{y}_{...})^2 \\
 &= \left(\sum_{K} \sum_{j} \sum_{i} (\underline{y_{ijk}} - \bar{y}_{i..K} + \bar{y}_{i..K} - \bar{y}_{...})^2 \right) \\
 &= \sum_{K} \sum_{j} \sum_{i} (y_{ijk} - \bar{y}_{i..K})^2 + 2 \sum_{K} \sum_{i} (\bar{y}_{i..K} - \bar{y}_{...})^2 \\
 &\doteq SS_{\text{within}} + SS_{\text{Between}}
 \end{aligned}$$

$$SS_{\text{Between}} = 2 \sum_{K} \sum_{i} (\bar{y}_{i..K} - \bar{y}_{...})^2$$

$$2 \sum_{K} \sum_{i} (\bar{y}_{i..K} - \bar{y}_{...})^2 = 2 \sum_{K} \sum_{i} (\bar{y}_{i..K} - \bar{y}_{i..K})^2$$

$$\begin{aligned}
 y_{ijk} &= \mu + S_{ik} + F_{j..k} + C_{j-1..k} + P_j + \varepsilon_{ijk} \\
 \text{sub } \downarrow \text{period seq} & \quad i=1:n_K \quad j=1:2 \quad k=1:2
 \end{aligned}$$

$$\textcircled{1} \quad P_1 + P_2 = 0, \quad F_R + F_T = 0, \quad C_R + C_T = 0$$

$$\textcircled{2} \quad \varepsilon_{ijk} \sim N(0, \sigma_e^2) \quad \text{i.i.d.}$$

$$\textcircled{3} \quad S_{ik} \sim N(0, \sigma_s^2) \quad \text{i.i.d.}$$

\textcircled{4} \quad \varepsilon_{ijk}, S_{ik} \quad \text{indep}

$$\hat{C} = \bar{U}_2 - \bar{U}_1$$

$$= [\bar{Y}_{12} + \bar{Y}_{22} - \bar{Y}_{11} - \bar{Y}_{21}]$$

$$= C_T - C_R$$

$$\sqrt{(\hat{C})} = \sqrt{2(\sigma_s^2 + \sigma_e^2)} \left(\frac{1}{n_1} + \frac{1}{n_2} \right)$$

$E(y_{11}) = \mu + F_R$	$E(y_{21}) = \mu + F_T$
$+ P_1$	$+ P_2 + C_R$
$E(y_{12}) = \mu + F_T$	$E(y_{22}) = \mu + F_R$
$+ P_1$	$+ P_2 + C_T$

$$\sigma^2_{\text{ME}}$$

$$2\mu + (F_T + F_R) + (P_1 + P_2) + C_T$$

$$- 2\mu + (F_R + F_T) + (P_1 + P_2) + C_R$$

$$\sqrt{Y_{i12} + Y_{i22}} = \sqrt{(2S_{i2} + \varepsilon_{i12} + \varepsilon_{i22})} = \\ = \sqrt{\delta_s^2 + 2\delta_e^2} = \underline{2(\delta_s^2 + \delta_e^2)}$$

$$\hat{F} = \bar{d}_1 - \bar{d}_2$$

$$d_{ik} = \frac{1}{2}(Y_{i2k} - Y_{i1k})$$

$$E(\hat{F}) = \frac{1}{2} \left((\cancel{P_2 - P_1}) + (F_T - F_R) + C_R - (F_R - F_T) - (\cancel{P_2 - P_1}) - C_T \right)$$

$$= \frac{1}{2} (2(F_T - F_R) + (C_R - C_T)) = (F_T - F_R) + \frac{(C_R - C_T)}{2}$$

$$\sqrt{(\hat{F})} = \sqrt{(\bar{d}_1 - \bar{d}_2)} = \sqrt{\frac{\delta_e^2}{2} + \frac{\delta_s^2}{2}} = \sqrt{\frac{\delta_e^2}{2}} \left(\frac{1}{n_1} + \frac{1}{n_2} \right)$$

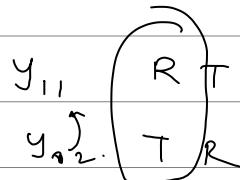
$$\sqrt{(d_{12})} = \sqrt{\frac{1}{2}(Y_{i21} - Y_{i11})} = \frac{1}{4} \left(\cancel{S_{i1} + \varepsilon_{i21} - S_{i1} - \varepsilon_{i21}} \right) = \frac{\sqrt{2}\delta_e^2}{4}$$

Use only period 1

$$E(\bar{Y}_{i12} - \bar{Y}_{i11})$$

$$= (\mu + P_1 + F_T) - (\mu + P_1 + F_R)$$

$$= F_T - F_R$$



$$\sqrt{Y_{i12} - Y_{i11}} = \sqrt{(S_{i2} + \varepsilon_{i12} - S_{i1} - \varepsilon_{i21})} \\ = \sqrt{2(\delta_s^2 + \delta_e^2)} \sqrt{\frac{1}{n_1} + \frac{1}{n_2}}$$

$$S_f^2 = \frac{(n_1 - 1) S_1^2 + (n_2 - 1) S_2^2}{n_1 + n_2 - 2}$$

$$t_{\text{stat}} = \frac{\hat{F}/c}{\sqrt{V(\hat{F}/c)}} = \frac{\bar{Y}_{i12} - \bar{Y}_{i11}}{\sqrt{S_f^2 \left(\frac{1}{n_1} + \frac{1}{n_2} \right)}}$$

⑤ prop

$$\textcircled{1} \quad n = \frac{\delta^2}{\alpha \cdot E^2}$$

$$\textcircled{3} \quad n = \frac{\delta^2}{E^2} \cdot (Z_{\alpha/2} + Z_{\beta})^2$$

$$n = \frac{2\delta^2 (Z_{\alpha/2} + Z_{\beta})^2}{E^2}$$

$$\textcircled{2} \quad n = \frac{\delta^2}{E^2} \cdot (Z_{\alpha/2})^2$$

two sided

$$n = \frac{\delta^2}{E^2} (Z_{\alpha/2} + Z_{\beta})^2$$

$$n = \frac{(\delta_1^2 + \delta_2^2) (Z_{\alpha/2} + Z_{\beta})^2}{E^2}$$

Effect	D.f.	S.S.	M.S.	F
Carry	1	$\hat{C}^2 \left(\frac{n_1 n_2}{2(n_1 + n_2)} \right)$	SS/Df	MS_{Carry} / MS_{Inter}
Inter	$n_1 + n_2 - 2$	$\sum_{k=1}^2 \frac{Y_{i,k}^2}{2} - \sum_{k=1}^2 \frac{Y_{..k}^2}{2n_k}$		MS_{Inter} / MS_{Intra}
Drug	1	$\hat{F}^2 \left(\frac{2n_1 n_2}{n_1 + n_2} \right)$		MS_{Dr} / MS_{Intra}
Period	1	$\hat{P}^2 \left(\frac{2n_1 n_2}{n_1 + n_2} \right)$		MS_{Pe} / MS_{Intra}
Intra	$n_1 + n_2 - 2$	$\sum_{i,j} Y_{ijk}^2 - \sum_{i,j} \frac{Y_{ijk}^2}{n_k} - SS_{Intra}$		
Total	$2(n_1 + n_2) - 1$			

