Clinical Trials

1. Subject : Healthy, Diseased individual ?
   Experimental Unit
   *
   *
   *
2. Treatment
   Drug * Tablet
   headache
3. Evaluation

~~Healthy~~ → sideeffect

AB → ____
A/B → ____
A ____ ____

food Weight gain → Chickens
→ ____
→ ____

Treatment :- Homeo, Allo, Aurvedic, → Unani
Physical Excercise
Teachi____ Psychologic ____
Parlour, Food ____
No treatment, Chemo, Radio
Surgical Procedures

Solid ____
Gas ____
Liquid ____

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

US-FDA - Food, Drug, Adminitration

Weight loose —— 80 → 60 min sideeffect →

Cost-optimization - Cost benefit

cost-eco pharmacoeconomics

Radiations - Genes ⇒ pharmacogenomics ✓

Evaluation

Pharmacology

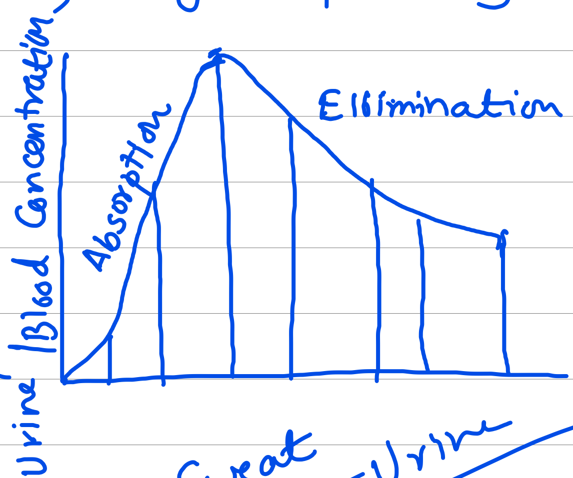
pharmacodynamics | pharmacokinetics

Drs. Clinicians

Drugs impact body

Drug administered & headache gone

body's impact drug



Sweat Urine

Spilker's Defn

Clinical Trial subset

Trials Phase-I

II

III

Piantodosi → Humans

Clinical Research → 10-12 → $drug_x$ → y_x disease

Pharma Co. CRO ✓ Clinical Research Organizations

| State Health Dept | CRI

Fund → preclinical trials ← Animals Tr.

sideeffects

x P(Death due to x) = 0.0001

Phase-I → 20/80 → sideeffects — min sideeffect

II → 800-1000 → effectiveness

III → Thousands → —— Physicans labelling

IV - Post Market Analysis

Life threatening side effects

pre clinical Trial - Animals →

Spilker Clinical Trials subset → Phase - I , 20-80 →

II 100-800 →

III Several Thousand →

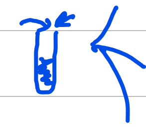
IV Post Market Study

Sample size estimator ↑

Piantodosi → human

Frog, Monkey ← Human

Sideeffects →



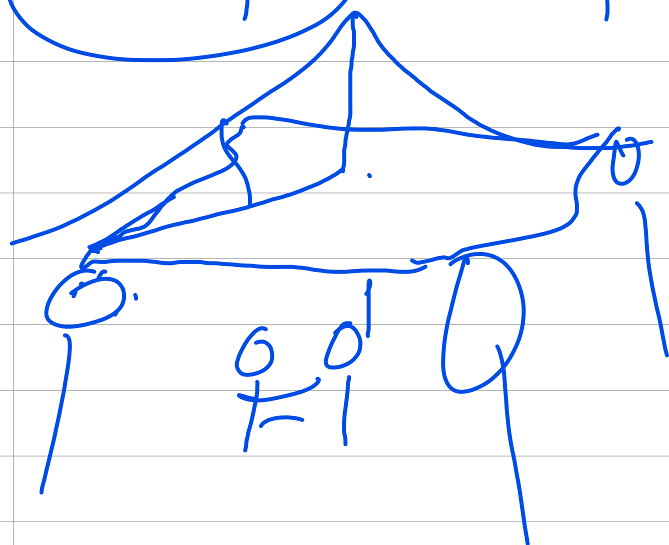
Titration Design

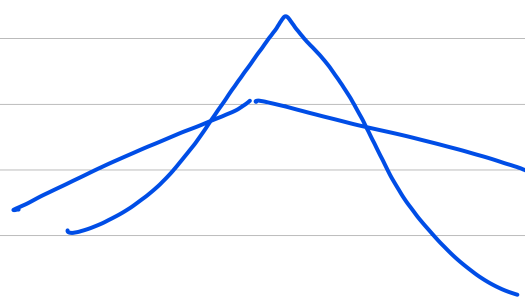
Dose-Response Relationship

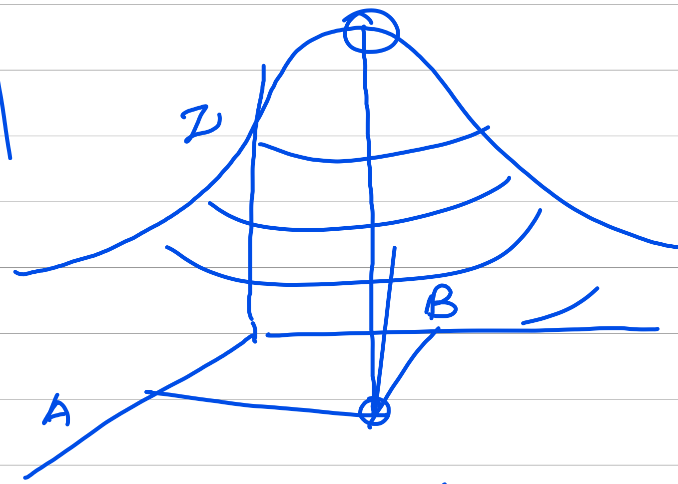
30 mg → ——

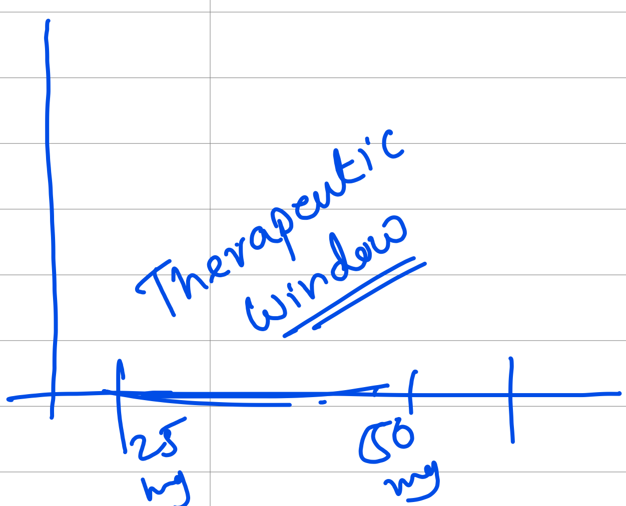
50 mg → —— + ↓ →

100 mg → —— +









10 mg

50 mg

80 mg

MED - Min^m Effective Dose

→ MTD → Max^m Tolerable Dose

0.00001 Life treatening side effect ← Physicians label

μ_p — Placebo ① ② ③ ④

μ_A — Active drug → ① Active Chemical effect
② Environmental factor
③ Body ← WBC/RBC
④ Physiological

$\mu_A - \mu_p$ actual effect of that ingredient

Statistical difference & Clinical diff

C_p ?

$\frac{USL - LSL}{36}$

LSL ? USL ?

Clinician / Doctors

SBP - DBP

80-120

50 - 90

low

30 80-120

A 90-130

A → $\mu_A = 105$, $\sigma_A = 1$

103 < > 108

80-120

Stat Significant

$B = \mu_B = 110$, $\sigma_B = 2$

98 — 122

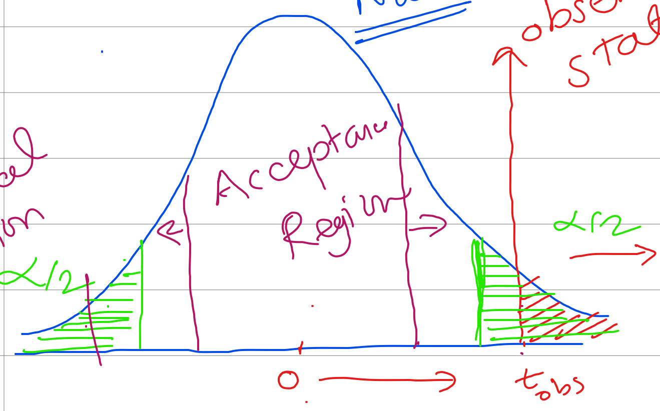
90-120

Clinician

under Null hypothesis

observed statistics

critical Region



$\alpha > p$

$p < \alpha \Rightarrow$ Reject H_0

$p > \alpha \Rightarrow$ fail to Reject H_0

confusion

Rohan Sir

Two way $\quad H_0 \Rightarrow \mu = \mu_0 \Rightarrow 2(1 - CDF)$

$2(CDF)$

One way $\quad H_0 :- \mu > \mu_0 \Rightarrow 1 - CDF$

$\mu < \mu_0 \Rightarrow CDF$

Patent $\qquad$ Generic Drug

Trademark filed (Branded) $\longrightarrow$ - Copied -

Active ingerdient (x) $\longrightarrow$ same (x)

Inactive ingre $\longrightarrow$ different

Millions

Research - Labs

↳ Paper (x) ⟶ disease $\qquad$ effective

Clinical Trial (CT) $\qquad$ Bioavaibility & Bioequi Trials (BA & BE)

preclinical $\qquad$ Patent $\qquad$ Biostatistician

~~Origi~~

CT $\qquad$ Ref

Phase - I

II

III

IV

10-12 years

market

x ⟶ Test ⟶ $\qquad$ $X + Y = Z$

Govt Health Dept

Clinical Research organization (CRO)

Pharmaceutical Company $\}$ ⟶ $\qquad$ Generic

1-2 years

BA - BE → Same dosage
strength
safety
Route of administrat

patent → generic

Commercial IND
① Pharma
Drug
Market
② Research → Market
③ NDA → Test

Non comm IND
① Sponsors → Dr / Physician
→ Govt
→ CRO ← NARI
ICR
→ ~~Pharma Co.~~
② ~~Market~~ Research
③ ~~NDA~~

Objective ① ~~Treatment~~ to reduce weight
② Immunity
③ Muscles

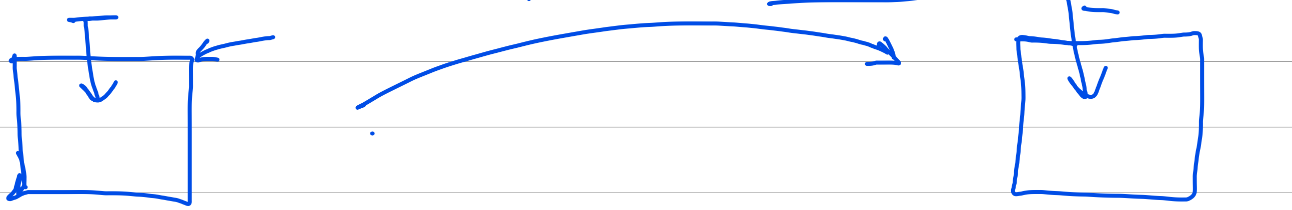
Objective ①
②
③
④

Object ① Fever ↓
② Cold ↓
③

effective or not
clinical endpoint
≤ 100

① Body temp
CFR
baseline → 100 70

FIR



① $H_0: \mu_T > 100$ $H_1: \mu_T \leq 100$ example

② $\mu_A = \mu_B = \mu_C$ H_1: at least one treatment mean differs

$H_1: \mu_i \neq \mu \ \exists\, i$

Inclusion & Exclusion for CTs

Exclusion

① < 18 & > 60 old age Exclude

② Feeding mother / Pregnant

③ History disease — Medications.

④ ___

⑤

Inclusion

Some

① Disease.

② Healthy volunteer

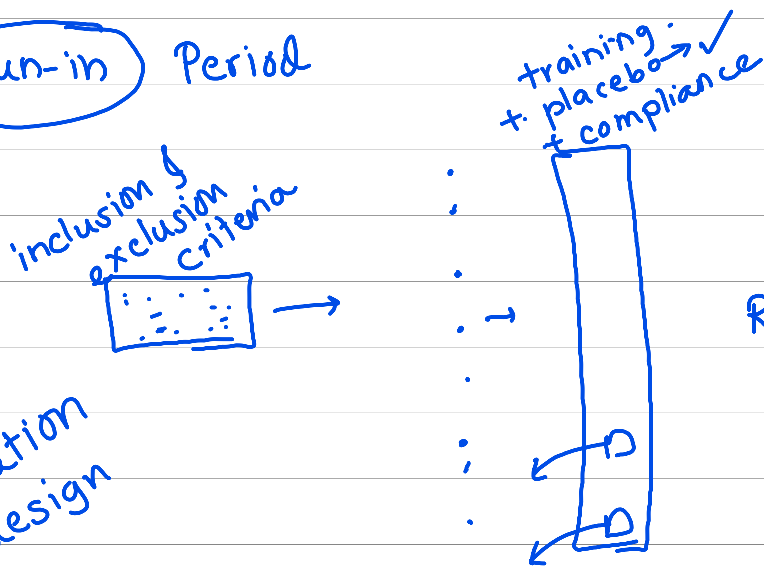
③ > 18

④

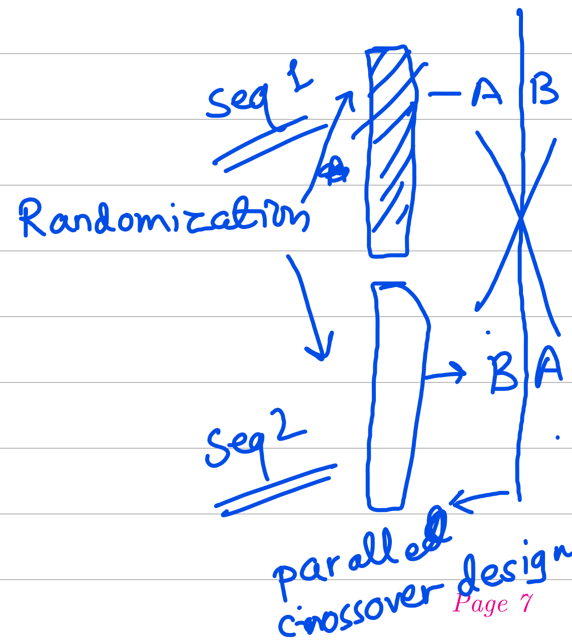
⑤

Some inclusion follow & all exclusion criteria not followed

Run-in Period



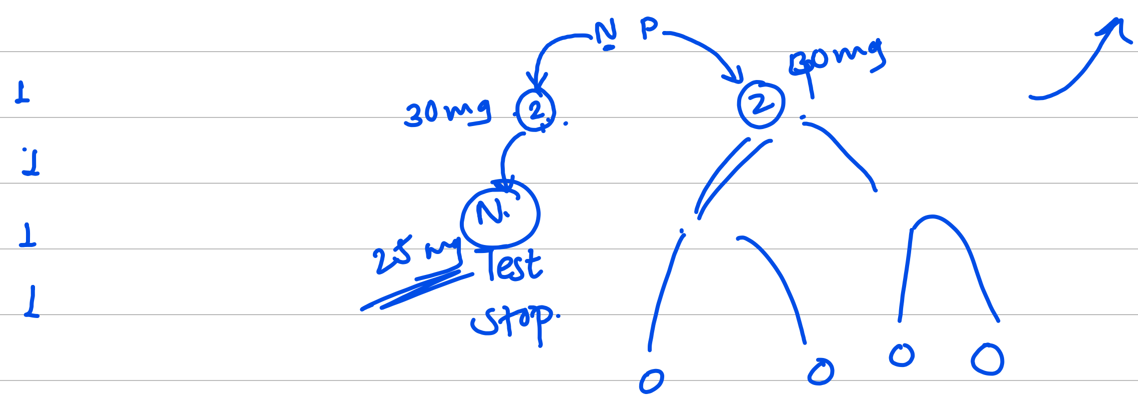
Titration design

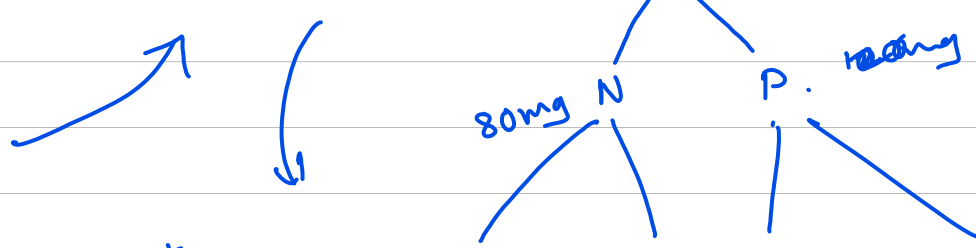


?. Titration design .

1. Upward
2. Upward-downward
3.
4. downward
5.
6.

Human Safety



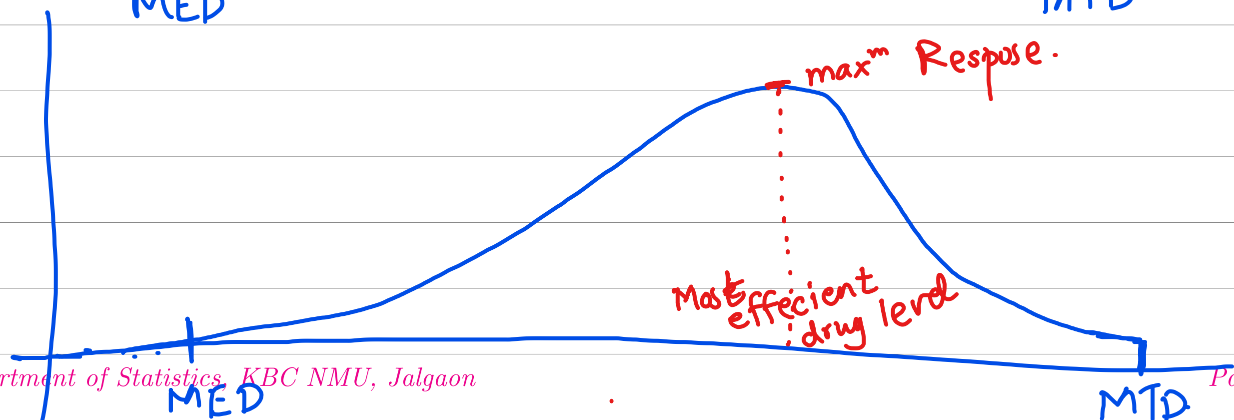


No effect ↓

25mg Therapeutic Window 100 mg

MED MTD

serious/ multiple side effects



① Methods of blinding

open label ① No - Everyone knows

② Single - Patient / Dr. any one is blinded

③ Double - & noone knows the allocations

④ Triple - Patient / Dr / Other staff all are blinded

↳ Data collectors - Nurse

Data ~~Analysts~~ - Statisticians

RCT FDA

Randomized, (single) double-blind

* Randomization

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

→ pop^n frame → sample

Randomization methods → Brain tumor patient → Trials

1, 2, . . . , 200

101

10

1, 2, . . . , 10

Randomization Assignment of patients to treatment groups

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

↳ Bernoulli (0.5) → 1 → A
0 → B

10 S → A, → B

① Complete Randomization

drugs
A & B · assign with equal prob.

Randomly
1 ·
2
3
100

*

using R ↘ SRSWR
① sample
② Bernoulli — 0.5 → 1 → A
0 → B
③ Uniform 0.5 < 1 A
> B

$\frac{n}{N}$ Sample fraction

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

30 → 10 → 12

No. of individual Risk ↓

A B C
100 10
fair?

Sample fraction should be $1/nD$ → $1/2$

Randomization ① Patient Pop^n → Random Sample drawn
Invoked pop^n
② Patient - Drug assignment

100000 → 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
A B A B A B ✓

A 1 4 6 ✓ $n(A) = 3$
B 2 3 5 ✓ $n(B) = 3$

(1 2 3 4 5 6) → Random Sample without replac

~~A A A~~

3 2 5 1, 4 6

A A B A B B

Bernoulli Sample

1	A	B
2	A	A ✓
3	A	B
4	B	A
5	B	A
6	B	B

21	1	6	B
22	2	3	A
23	3	2	A
24	4	4	B
25	5	1	A
26	6	5	B

3

Forced Sample fraction = $1/n_D$

1-3 → A

4-6 → B

* Complete Randomization

nA

A → 01

B → 19 / out (20) patients] not comparable group

n_m~

↳ Balanced ⇒ 10 sub A & B each comp

↳ Imbalance ⇒ $P[n_A \neq 10] = 1 - P(n_A = 10) = 1 - {}^{20}C_{10}\, 0.5^{20}$ =

Prob.

$n_A \sim$ Binomial Distribution (20, 0.5)

* Permuted block Randomization.

To avoid Treatment imbalance

Forcefully Treatment balance

30 patient divide in 3 blocks

$6:10 = B$

$1:5 = A$

$n \to B$

$\frac{n}{2}+1 : n$

$1 : n/2 \to A$

$n \to \frac{n}{2}$

1	1	10	B	11	1	21	1
2	2	2	A	12	2	22	2
3	3	8	B	13	3	23	3
4	4	7	B	14		24	
5	5	6	B	15		25	
6	6	3	A	16		26	
	7	4	A				
	8	1	A				
	9	5	A				
10	10	9	B	20	10	30	10

→ Do this procedure For all blocks → Then Combine

↑ Permutation of 1 : blocksize

nA=5
nB=5

Stratification

block size → 30 patients divided into 3 blocks

what if I want only 2 blocks

?

1	1		16	1
2		8-A / 7-B		7-A / 8-B
15	15		30	15

30 → 1

5 → A

5 → B

10

nA=15
nB=15

Suppose we have 99 no. of patients & two treatments

→ Balance impossible ⇒ Create dummy patient ✓

99 + 01 = 100

1 1 99

90

90

potential bias

B = 50

A = 49

100, 100 D3 A

* 6 blocks

I have used permuted block Randomized here.

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

~~58~~ 60

Treatment Com balance perfect

		A	B
		5	5
5	M	5	0
5	F	0	5

~~comparable groups~~

Adaptive Randomizations

1. Treatment Adaptive Randomization
2. Covariate A R (Stratified Randomi:)
3. Response A R

50 → Two blocks mB - fB

Gender
+ Smoking
+ dr.
+ treat cond^{a}

mB: A / B → 40 → Permuted block → nA 20, nB 20

fB → 20 → A 10, B 10

* Covariate :- Strata → Covariate - Seq^{n}s - 6 - SF (B-3, A-3), 6 - SM (A-3, B-3), 4 - NF, 4 - NM

Covariate. Groups - ✓ ~~Permuted~~ ~~C~~omplete - Randomiz.

* Treatment Adaptive Randomization

	A	B		
1	1/2	1/2	A	A → fraction of individuals
.	1/2	1/2	A	receiving A may ↑
.	1/2	1/2	A	imbalanced
20				

equal prob. independent

Efron (1971) Biased coin randomization

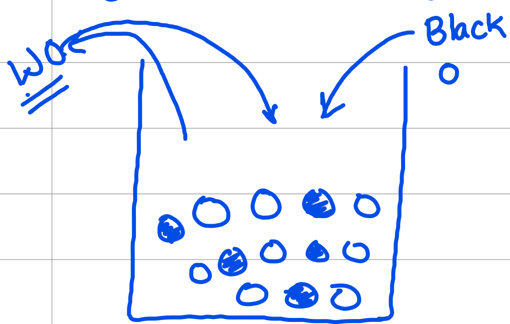
	A	B	
✓ 1	$1/2$	$1/2$	A ✓
2	$1/2 - 1/20$	$1/2 + 1/20$	A
	$1/2 - 2/20$	$1/2 + 2/20$	B
	$1/2 - 1/20$	$1/2 + 1/20$	

$p = q = 1/2$

p	q	A
$p = p + 1/20$	$q = q + 1/20$	A :
$p + 1/20$	$q = q + 1/20$	

20

Urn Randomization



White	Black	P(W)	
A=15	A=15	$A/2A = 1/2$	
A	A+1	$A/(2A+1) < 1/2$	$\underline{\underline{30}}$
A+1	A+1	$1/2$	

Balance $\begin{cases} 1 :- W \to A ✓ \\ 2 :- B \to B ✓ \end{cases}$

~~Ia~~ T A R code

no. of patients :- 30 ~~A=15~~ 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
}
```

* Respose Adaptive Randomization

(Play the winner —)

Without Replacement
Respose Adaptive
2days treatment

play the winner

Complete, PB Str
CovAR TaR

	A	B	SD	
1	nA	nB	A → + : ✓	
2	nA+1	nB-1	A → − .	
3	nA	nB	B → − :	
4	nA+1	nB-1	✓ .	

play the winner

Randomization

1 : A
30 : B

→ 2 days.

2 days × no. of patients

Time consuming

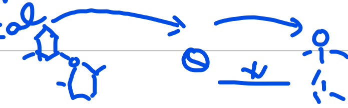
→ Phase-I → First time human trials
safety concern → Effecacy not proven so far.

nA+1 nB-1 ← A+ / B−
nA-1 nB+1 A− / B+

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.

preclinical



Phases- clinical trials

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

mostly healthy 20-80 subjects

II First time- well controlled* CT. ① effectiveness & safety ② Dose-Respose Rel^n

100-<1000 IIA several hundreds subjects - Dose Range

IIB several thousands ✓ extended phase II trials - Effectiveness

III controlled & uncontrolled trials → Physcians Label

several thousands

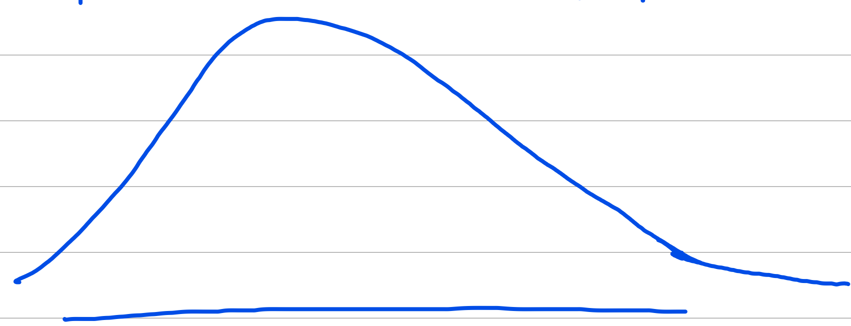
↳ Additional info effectiveness & safety needed to identify benefit-risk relationship ⇒ Drug Approval → Process submission → Trials → Phase IIIB ✓

IV After drug approval → Post market trials → Adverse Effect

Competitive — morbidity of mortality

other 18-60 patients

*ADME :- Absorption, Distribution, Metabolism, Excre



* Titration :- designs

1000 → Drug A → 50-60 died.

↳ instead → use 1 patient → obser

side → 1 ; L high

2 side → lower ; 1 → same

MED & MTD ?

Min^m effective tolerable

MED Therapeutic window MTD

* Control ? :: Treatment

Ref :- ① No treatment
② Placebo treatment
③ Active Drug
④ Dose-response concurrent
⑤ Historical concurrent

Test Drug → Control group. Ref

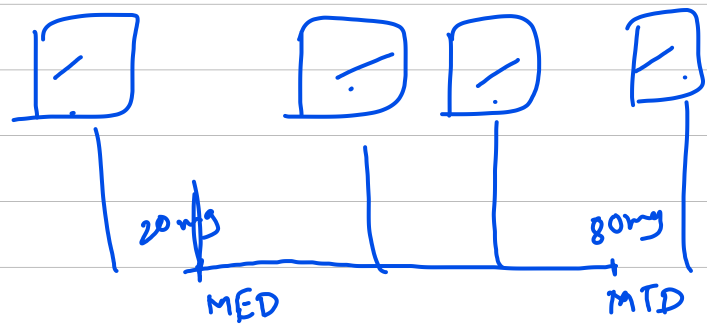
Drug is effective (Therapeutic window)

concurrent control

Test

parac

Rare disease :-
eg. Brain tumor 10-12 patient
1985 assume
No. patient



* Safety :- Test

P(Death/Test) = 0.0000001

Phase-I ⊢ 20-80 → may not observed
II 100-1000 → may

* Investigational New Drug :

Commercial IND	Non-commercial IND.
① Leads to NDA	① May or may not be
② Market purpose	② Research purpose
③ Pharmaceutical companies sponsor	③ Sponsors.

* NGOs
* Govt Health dept (NARI, Cancer, I)
* CROs
↳ 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

$\boxed{\text{Protocol}}$ ← FDA Follow.

endpoint
Inclusion.
Randomization
Tre
obs
drug.
clinical.
Analysis.
P/α

Routes of Administration of drug
1. Oral
2. Veins Intravenous
3. Arteries
4. Nasal
5. Muscles. - Intramuscular
6. skin
7. ______
8. ______

1. Oral
2. Sublingual
3. Rectal
4. Topical
5. Parental Intravenous
   - Intramuscular
   - subcutaneous

Center Test Sub
14 01 001

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 ✓ 8am ✓ 10am 12 noon missing obs. ✓ 2pm

1 — 9 mont

③ 7 pre Premature Termination.

④ I II.

* Multicenter Trials :- ?
① No. of ~~pat~~ subjects ↑
② Results generalizable

* Interim Analysis

0 15 30 days

Results → outside Statisticians

Absent :- 2001, 4, 6, 12, 14, 16, 17, 18, 22, 25, 33, 34, 35, 43, 44, 45, 47, 50, 54, 55 = 20 students

Thank you.

Patent Generic. ✓

Para + X form Para + Y form

Route of administration

ANDA

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:-	0 mg	250 mg ✓	500 mg
	Placebo	A	A
	1 →	1 →	1 →

Drug Patient

4 measurements

A → 1 → $x_{11}\ x_{12}\ x_{13}\ x_{14}$ ← Repeated Measurement ~~2 3 2 2 2 4~~ → 2 3

B → 2 $x_{21}\ x_{22}\ \ x_{24}$

C → 3

Note Effect → then Anova

- Repeated Measurement
- Replications ? same treatment on diff. individuals

Drugs	Patients	
A.	1, 4	2
B	2, 5, 8	3
C	3, 6, 7	3

Replication

① One-way A B C $\mu_A = \mu_B = \mu_C$

io

A → Group 1 n_1
B → 2 n_2
C → 3 n_3

homogenous Group formation? Comparable ~~Uniform~~

↳ Randomization ? Unbiased

↳ Reduce bias & variability

Anova :- F dist^n

$F_{\alpha, r-1}$

$F_c < F_{table}$

Fail to Reject

✓ $\mu_A = \mu_B = \mu_C$

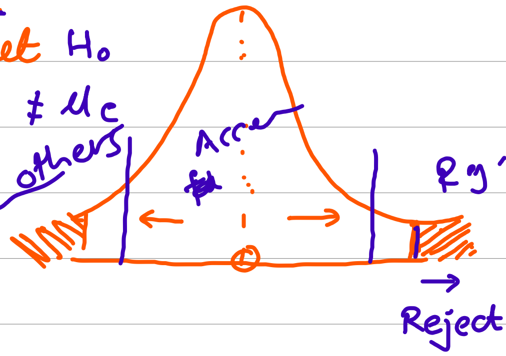
p value

$p < \alpha$

↳ Reject H_0

at least $\mu_A \neq \mu_B \neq \mu_C$

one treatment differ from others



Post-hoc

Pairwise Comparison

μ_A μ_B μ_C

① $\mu_A = \mu_B$

② $\mu_A = \mu_C$

③ $\mu_B = \mu_C$

Bonferri / 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

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

A - 10
B - 12
C - 9

② Two-way

Two factors - different levels

① Smoking habits

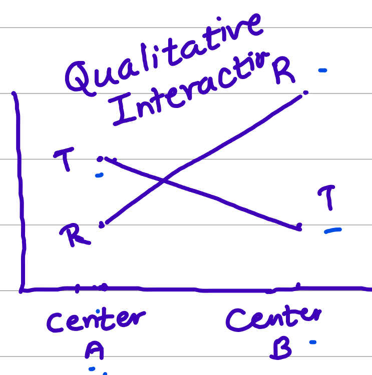
②

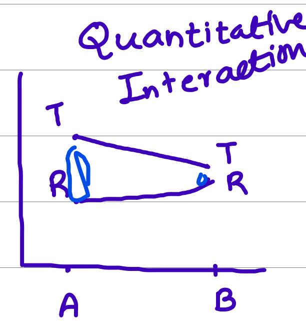
Gender	Smoker	Non smoker
low	n_1	n_2
Moderate		
high		

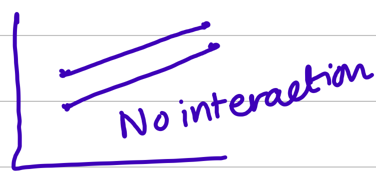
→ r /obs per cell

③ General two way

Interaction Effect







④ Factorial Designs? -

2^K factorial ← levels.

↑ No of factors

2^3

	B_1	B_2	B_3
A_1			
A_2	✓	✓	
A_3			

Two-way with inter

~~Treat~~ Row

Col

Inter -

Er

Row	$r-1$
Colu	$c-1$
Inte	$(r-1)(c-1)$? → sign
Error	
Total	$\boxed{}$

→ $\hat{\sigma}^2$

error → MSE

$n-r-c$

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

Interaction

effect identify

Confounding ?

- due to some identified/unidentified factor effect

CRD 1, RBD 2, 3 Factorial

LSD

Latin Square Design

3 factors

Columns

Rows -

A	B	C
B	C	A
C	A	B

A	B
B	C
C	A

Balanced Incomplete Block Design

Designs CT

Obs: ① Test treat > better Refere

Control :-

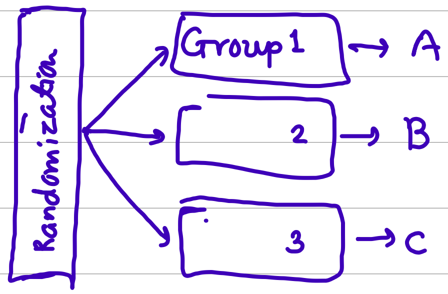
Active Concurrent Controls

① Objectives — Treatment

② Other Factor — clinical endpoint

③ Design — Analysis

* Parallel Group Design   3 treatment A, B, C



Categorical

Run-in Period
Training

Analysis ? ① Anova
Assumption Normal
② Cat Anova
③ χ^2
④ ___ Nonparametric
___

Homogenous

2 treatment ① t-test
② χ^2
③ Nonparametric

Matched Pair

5, 4, 3, 2, 1 →

	A		B	
160-165	1	⟷	3	160-165
150-155	2.	⟷	5	150-155
185-190	4	⟷	6.	

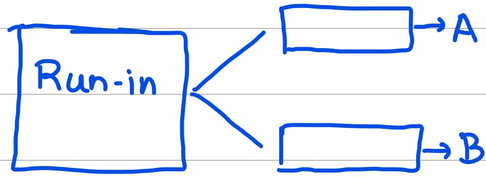
{1, 3}
{2, 5}
{4, 6}

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

Variability → Intersubject - Between - Patients
→ Intra subject - Within - Patient

Variability → Intersubject :- ~~Single~~ Same treatment → diff sub → diff responses
variation.
→ Intra subject :- Same treatment → same patient - diff time points
within patient

Parallel Design



comparison

1-100 → n_A patients – Drug A estimator μ_A σ_A ← Intersubject ✓

101-200 → n_B – Drug B μ_B σ_B ← . . .

Replications

Period I — Period

1-100 → A — A

101-200 → B — B

Intrasubject

3

1 month — 1 month.

Drawback

Intrasubject variability is not estimable in PD.

Run-in Period

Recruitment → A → B

① Training ✓

SC

7-7:30 → 8 – blood n

Drug A → hour Low/ Mode/ High

② FIR – baseline variable

↳ Covariate

↳ Inclusion Exclusion Criteria

103° F → 99 F

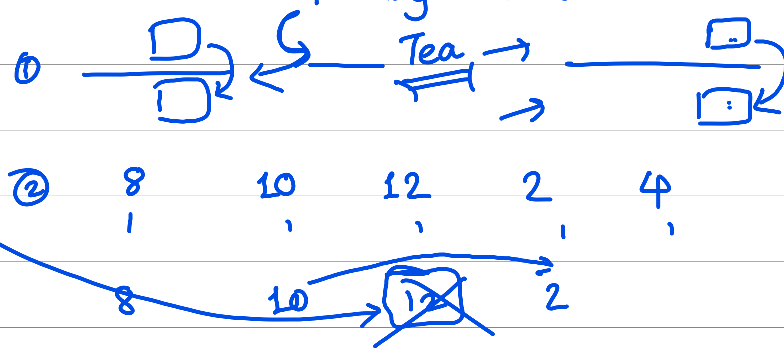
baseline ✓ Clinical endpoint

③ Placebo respondent identify

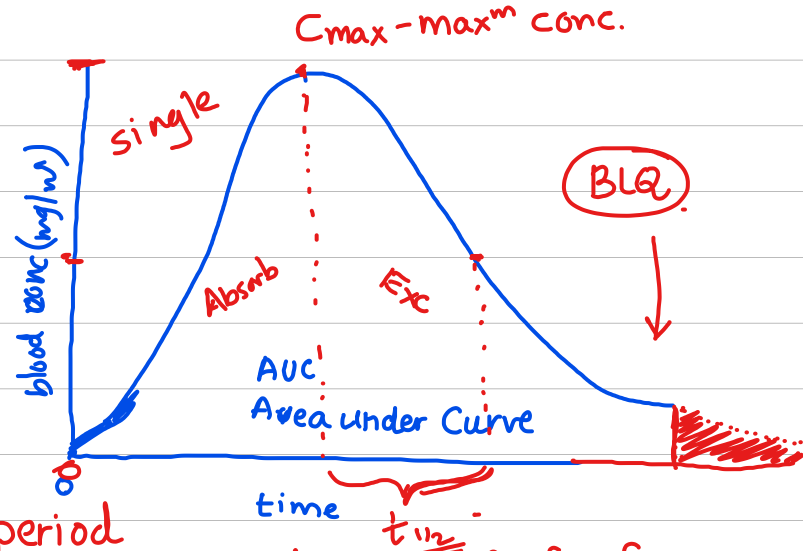
④ Patient compliance

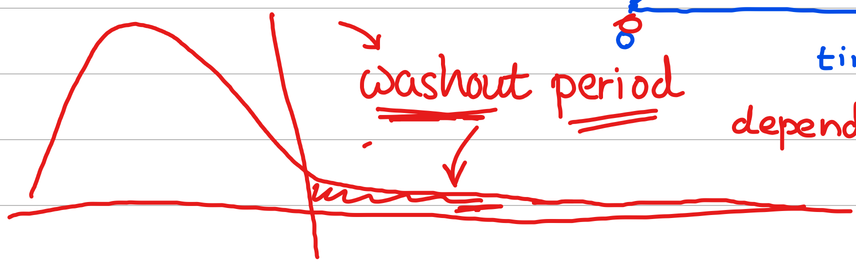
Nil by mouth

✓ ⑤ Washout period for previous treat



Phases → Drug ADME





washout period

depends on half life of a drug

$t_{1/2}$

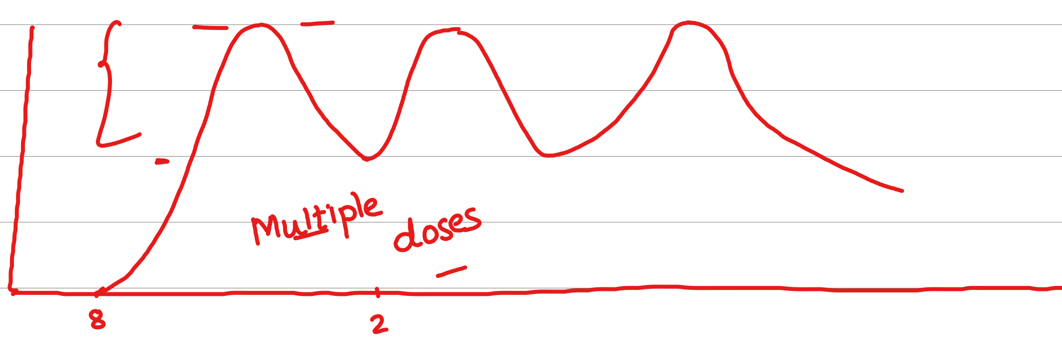
$6 \cdot t_{1/2}$ treatment duration

Prayers Run-in | Period 1 10:30 - 12:30 Treat 1 | Washout 12:30 - 2:00 | Period 2 2:00 - 4:00 | Treat 2

8 2 8

Nurse 8 - 2 - 5 → 8

3 ← MED - MTD



Treatment Effect ① Active ingredient] X I
② Placebo
③ Dise Life
④ Other factor

✓Cluster Randomized design

ST-103

Cluster Sampling ?

3000 → 10 → ⑤ ⑤

Group A

Group B

within high

between low

Cross-over Designs

Run-in Randomization

Group 1 – A (1:50) — Period 1 — Washout — Period 2 — B

Group 2 – B (51-100) — washout — A

8m 1month 8m

p q

2×2

	Period 1	2	3	4
1:50	A	B	A	B
51:100	B	A	B	A
	8m	1m 8m	1m 8m	1m 8m

μ_A intrasubject

Complete Crossover

1 → A B B B

2 → B A B A

$$\begin{array}{c|cc} & 1 & 2 \\ \hline 1 & A & B \\ 2 & B & C \\ 3 & C & A \end{array}$$

$$\frac{p \times q}{3 \times 2}$$

Seq^n period

L-RT
2-TR

R	T
T	R

T R

$$Y_{ijk} = \underset{\text{general mean effect}}{\mu} + F_{(j,k)} + P_j + \underline{\underline{S_{ik}}} + C_{(j-1,k)} + \underline{\underline{\varepsilon_{ijk}}}$$

subject, period, seq^n — Random — washout period — Random

Summer — Winter

	Period 1, $j=1$	Period 2, $j=2$	
Seq^n 1 ⇒ $k=1$	$E(Y_{\cdot 11}) = \mu + F_R + P_1$	$E(Y_{\cdot 21}) = \mu + F_T + C_R + P_2$	$1 : n_1$ (n_k)
Seq^n 2 ⇒ $k=2$	$E(Y_{\cdot 12}) = \mu + F_T + P_1$ $E(\bar{Y}_{\cdot 12} - \bar{Y}_{\cdot 11}) = F_T - F_R$	$E(Y_{\cdot 22}) = \mu + F_R + C_T + P_2$ $E(\bar{Y}_{\cdot 22} - \bar{Y}_{\cdot 21}) = F_R - F_T + C_T - C_R$	$1 : n_2$

2×2

add^n E: $F_R - F_T + C_T - C_R - F_T + F_R \Rightarrow 2(-F_T + F_R) + (C_T - C_R)$ ✓

Random Effect Models — Fixed effect Models

$$Y_{ij} = \underset{\text{fixed}}{\mu} + \underbrace{\alpha_i + \varepsilon_{ij}}_{\text{Random}} \qquad Y_{ij} = \underbrace{\mu + \alpha_i}_{\text{fixed}} + \underset{\text{Random}}{\varepsilon_{ij}}$$

$P_1 + P_2 = 0$, $C_R + C_T = 0$, $F_R + F_T = 0$

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

$S_{ik}, \varepsilon_{ijk}$ indep.

$\cancel{C_R - C_T}$ $\quad C_T - C_R$ = Carryover effect.

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

Cross-over design $\quad p \times q$ (period, seq^n)

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

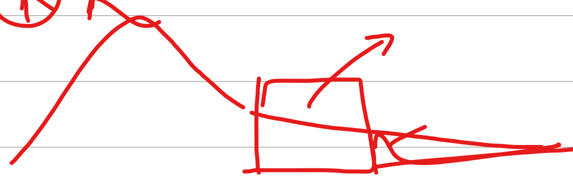
1m 8m | 1m 8m

1 A
2 B

Fever - $103^\circ \xrightarrow{R} 99^\circ$ $103^\circ \xrightarrow{T} 98^\circ$

R T

R R



Interview, Case Study

Absent :- 2003, 6, 9, 10, 15-17, 25, 30, 35, 39, 43-47, 51, ∴ = 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

3×3 Std. Crossover design

$\underset{\text{seq}^n}{p} \times \underset{\text{no. of periods}}{q}$

$p = q$

Higher order crossover design $p \times q$ no. of treatment t

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

① Treatments :- A & B $t = 2$

	1	2	3
$\boxed{1}$	A	B	B
2	B	A	A

$q = 3$

$p = 2$

2×3 $t \geq 2$

②

	1	2
1	A	B
2	B	A
3	A	B

3×2

Sik

3 treatment

1	A	B
2	B	C
3	C	A

contrast ?

$\hat{\mu}_A - \mu_B \overset{?}{=} 0$

$\hat{\mu}_B - \mu_C \overset{?}{=} 0$

$\hat{\mu}_C - \mu_A \overset{?}{=} 0$

$v(\hat{\mu}_i - \mu_j) = \delta^2 \quad \forall i, j, i \neq j$

balanced variance (Same)

↳ Balanced design

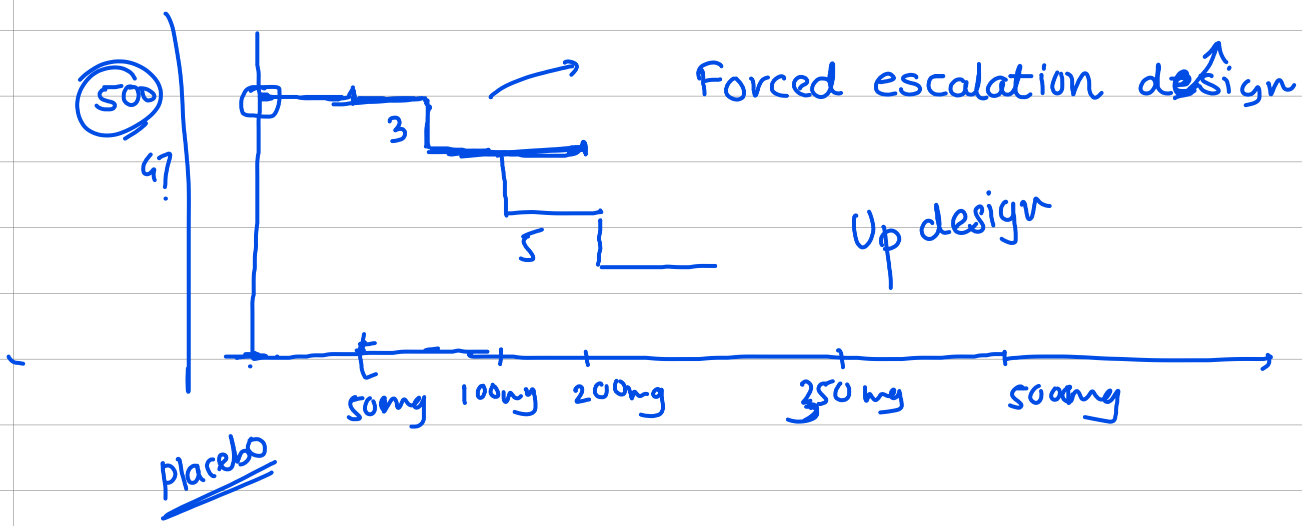
Williams

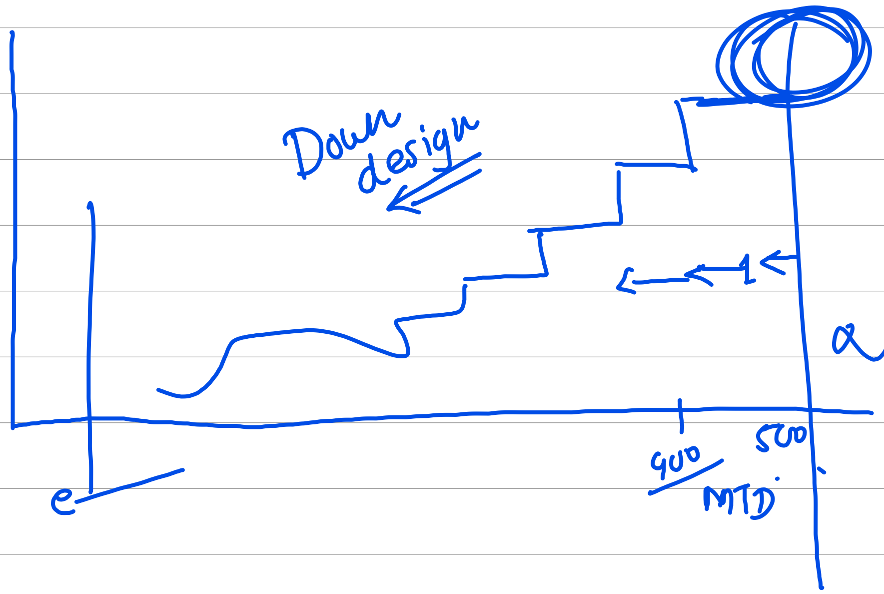
A B C D
B C D A
C D A B
D A B C

Titration Designs

Phase-I trials safety - evaluation
II

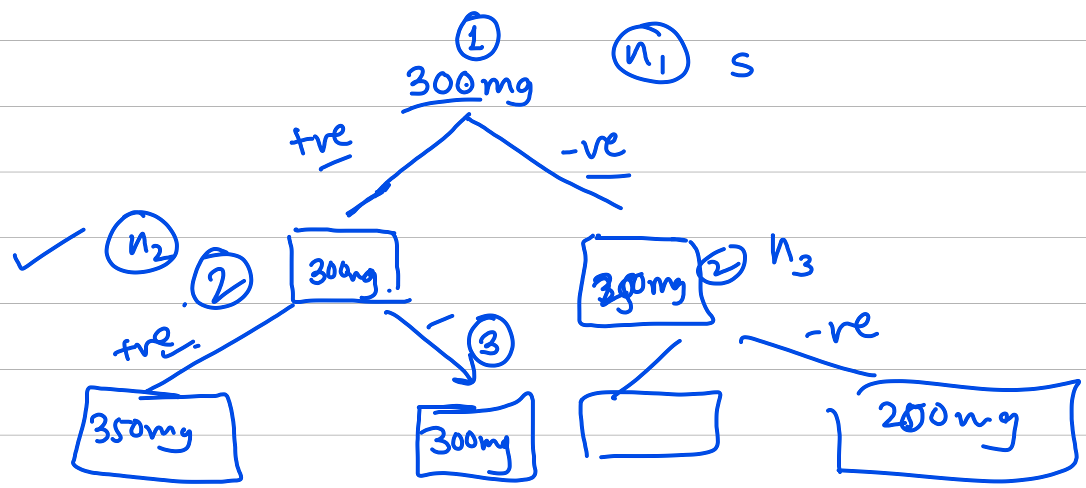
Titration. Theurapetic Window [MED - MTD]





Flowchart

A, B, D



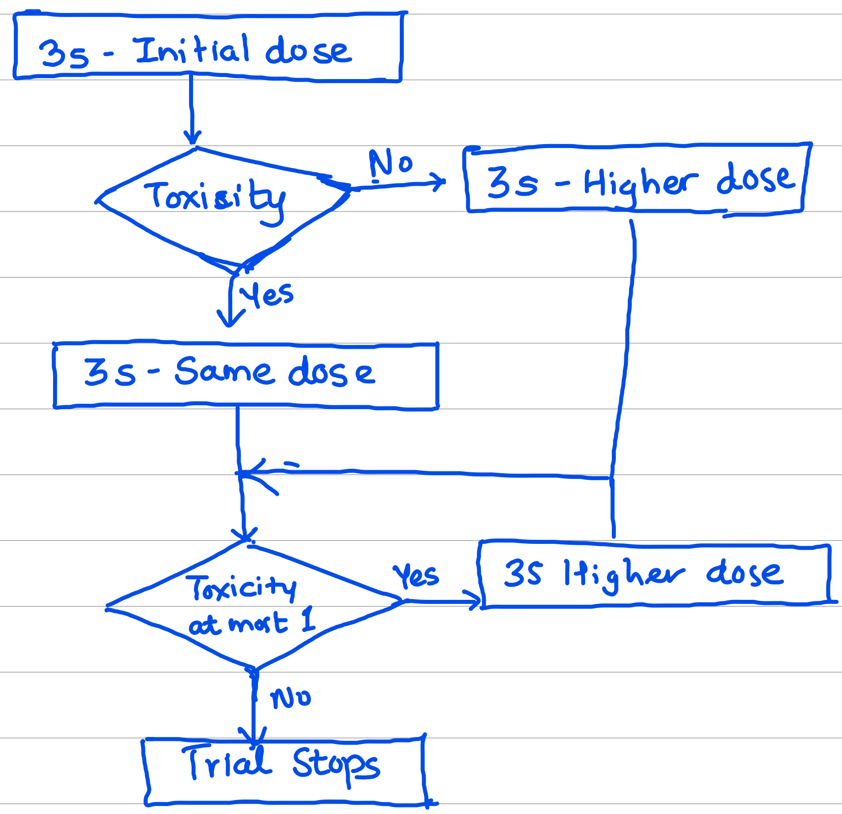
min^m effective dose max^m tolerable dose

Dose- Response ~~Re~~ Trials

1. Parallel Dose Respose
2. Crossover
3. Forced Titration
4. Optional Titration

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

Flowchart Design A Up ↑

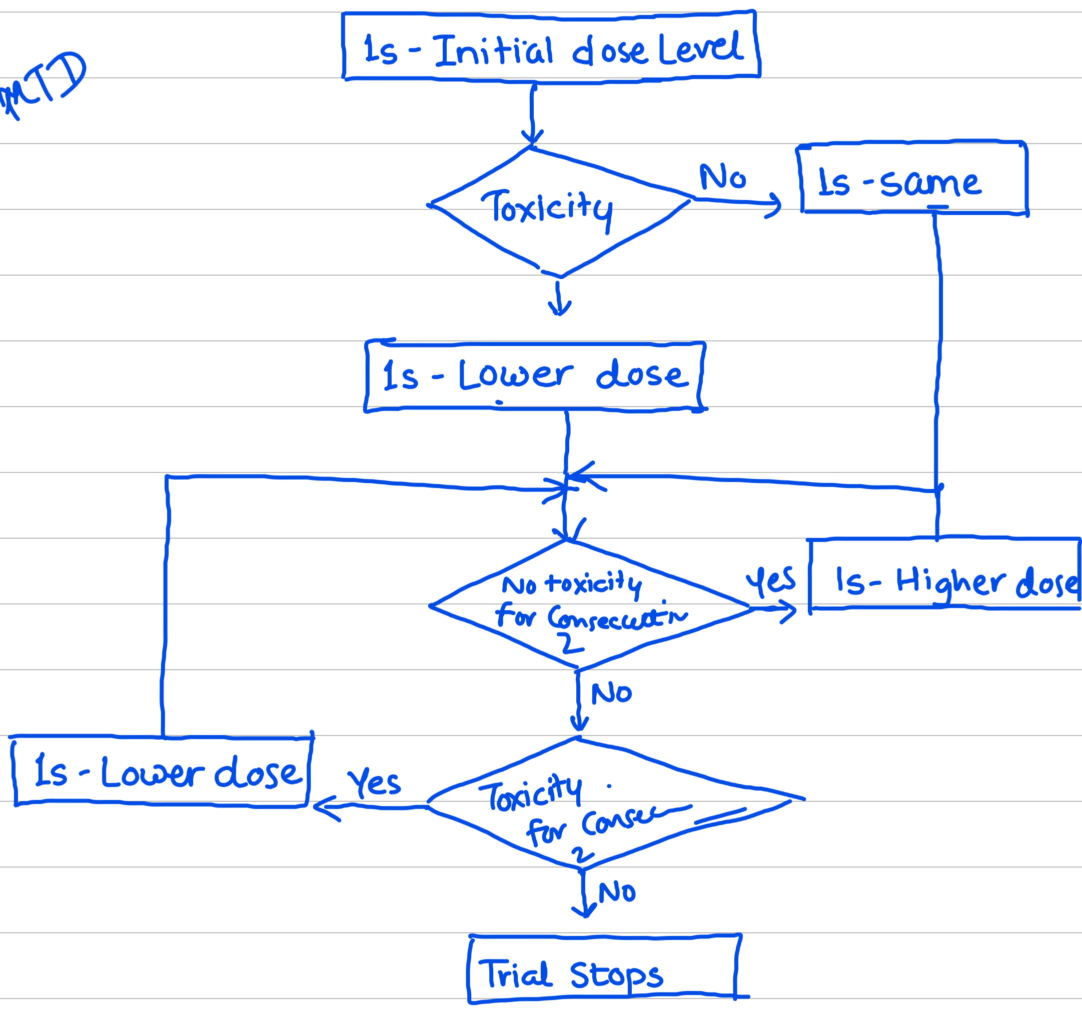


Flow

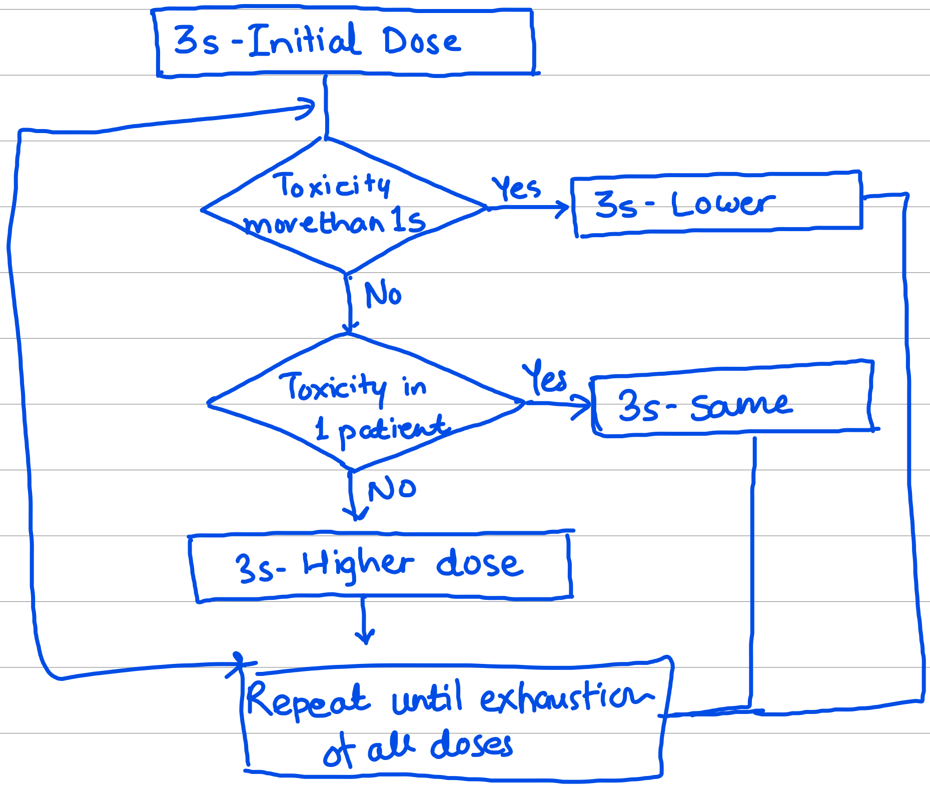
MED

Flowchart for Design B down ↓

MTD



Flowchart for Design D :-



Classification of CTs

① Multicenter Trials :-

② Superiority Trials :- Test Ref ← placebo, No.

$\mu_T \geq \mu_R$

③ Active control :- $\mu_T \geq \mu_A$ ← active drug

Non-superiority → Equivalence trial

$\mu_T = \mu_A$

→ Variance Bioequivalence ✓

→ Average Bioequivalence ✓

④ Dose-Response Trials :-

↳ ① Randomised Parallel Dose Design

② Cross over Dose Response

③ Forced titration dose-escalation

③ Placebo-controlled

⑤ Combination Trials :-

↳ Combination of active ingredients.

⑥ Vaccine ?

↳ ① Superiority Immunoge_____ trial

② Dus-Res I

③ Cro

④

⑤

① Multicenter Trials ?

Why? i) Generalization -

② Treatment by center interaction ✓

③ Sample size

(i) Generalization

① → Subject Re...itment Rare - Brain-tumor - 20-25.

①

②

③

sample size ↗

estimator

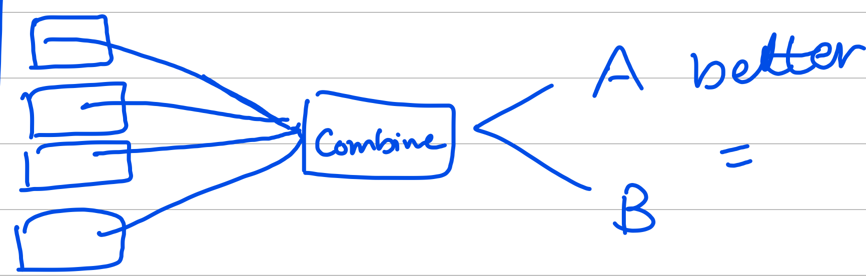
comparable group.

② Homogenous

Multicenter.

Center	Better
1 →	A ✓
2 →	A ✓
3 →	B ✓ 3/4
4 →	A ✓

A



- Background
- Career opportunity
- Industry Exp.
- Role of data Scientist

Stat. Comp domain Manage.

Python

RF

XGbm

Neural

Regr.

Clustering Unsup

Govt

- ISS
- RBI
- State
- Sb
- ST
- Research

Corpo

- Bio
- Data
  - Retail
  - Banking
  - Product

Gender – M / F

DP

Age – 18–60

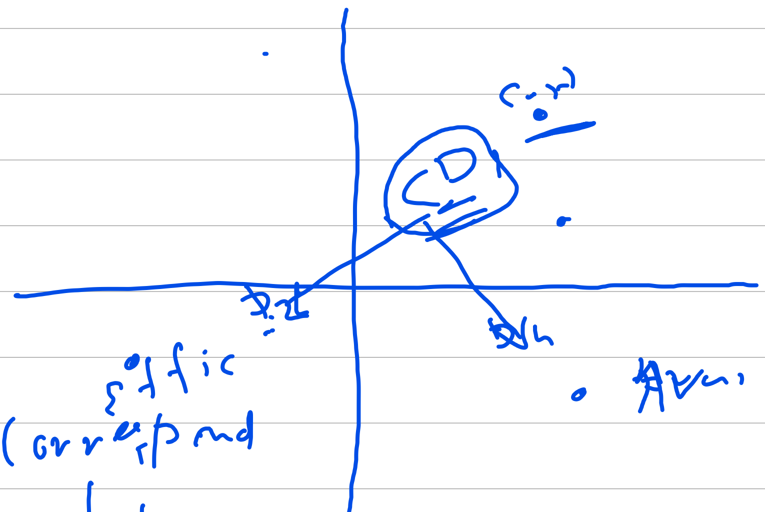
99

Taste
Color
Package

18–25 25–35 45–60

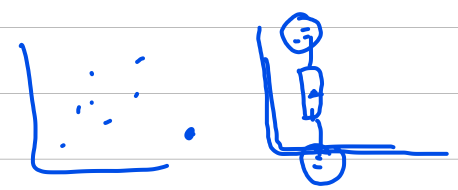
	Cost	Avail	Eff.
CD	1	2	5
D1	3	5	4
D2			
D3			
D4			

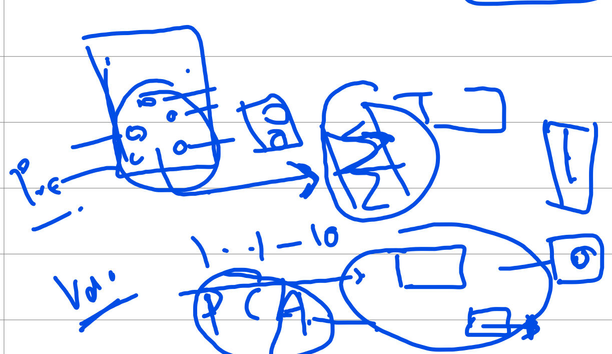
1 – 5

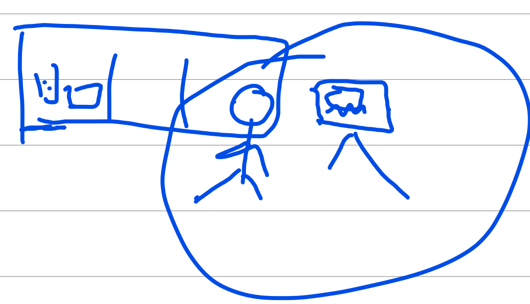


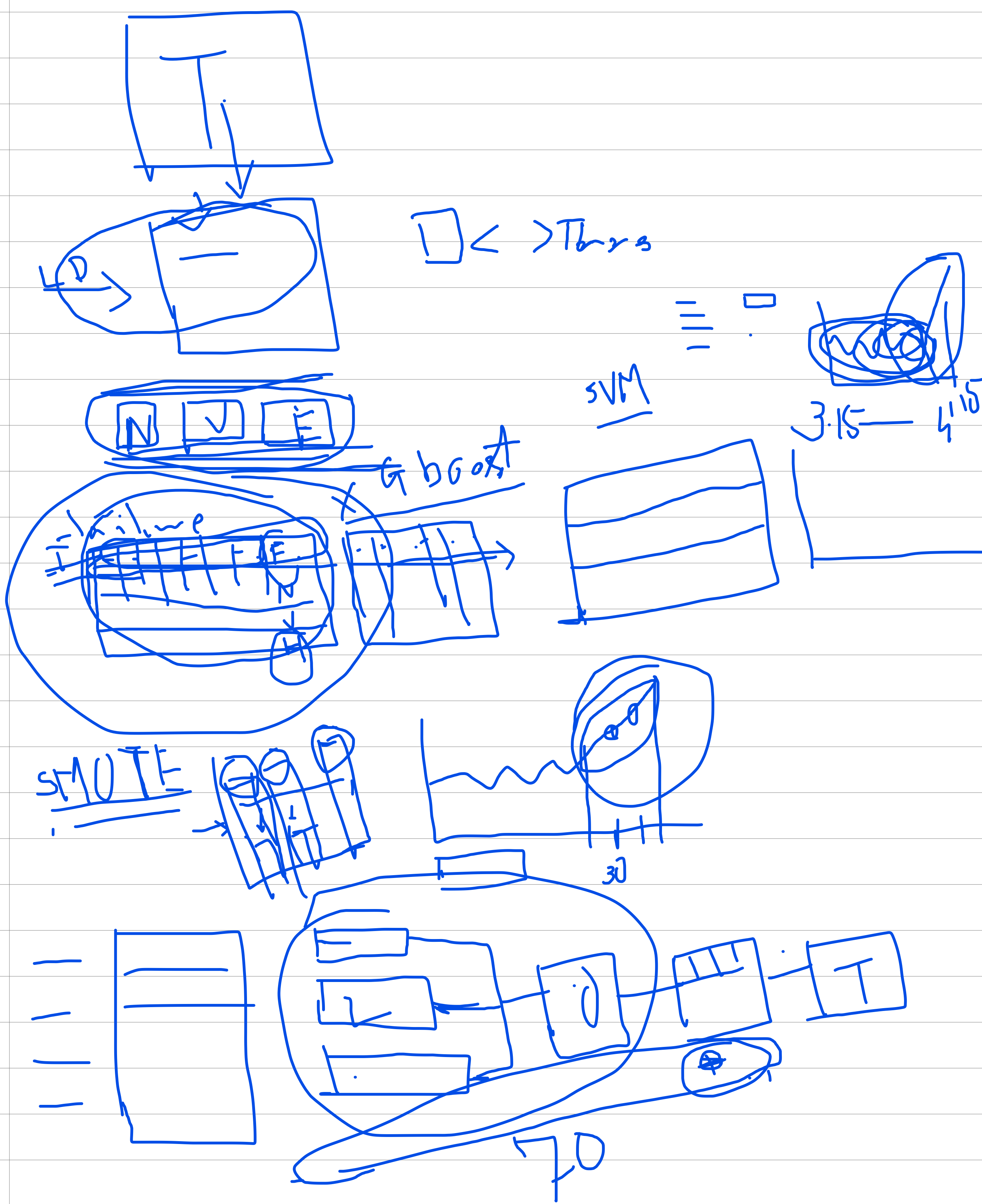
Specific
Correspond

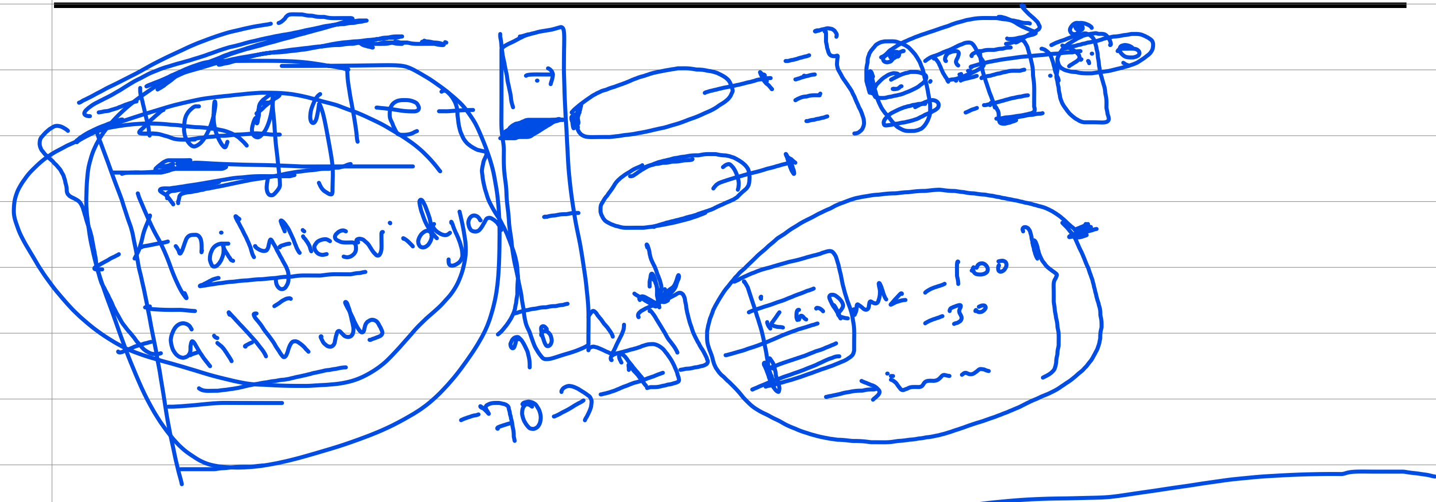
Anomaly








SVM
3.15
SMOTE
30
70



Knowledge Transfer

* Repeated Measure

Age	Treatment	DBP0 (at time of dosage)	DBP1 (1 week)	DBP2 (2nd)	DBP5 (5th week)	Gender
✓	A	Baseline $\boxed{4}$				✓
	B					

$\boxed{\text{ANCOVA}}$ KKK

GLM

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

GLM → Regression

One Way — Regression

$y = \mu + \alpha_i + \varepsilon_{ij}$ — $y_i = \beta_0 + \beta_1 x_i + \varepsilon_{ij}$ — $Y = X\beta + \varepsilon$

Non full rank — full Rank — ANOVA: Indicator variable — Regression: Physical variable

? individual parameter — not esti — esti ✓

② Random Effect model

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

$$\alpha_i \sim N(\alpha, \sigma_\alpha^2)$$

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

Fixed Effect

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

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

③ Two way model

Column

Row

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

Nested Design

	Supplier 1			Supplier 2			Supplier 3		
Batches	1	2	3	1	2	3	1	2	3

Obs. y_{111}, y_{112}, y_{113} ... y_{311}, y_{312}, y_{313} ... y

Batches nested under suppliers.

Blocks / Batches

	1	2	3
Supplier 1	3	3	3
2	3	3	
3	3	3	

r-obs/cell two way setup

Not equivalent why?

Parallel Group

Seq A → Sub 1, 2, ..., n

Seq B → 1, 2, ..., m

subjects are nested under seq^n

nested design

Minitab :-

Y_{ij}	Sub	Seq^n	Peri	Drug + c	μ +
	1	1			
	2	2			
	3	1			
	⋮	⋮			

SAS ✓ model Y = Drug Seq^n Period Sub(Seq^n) + carry

nested

Seq^n 1 — sub 1

Nested

Seq^n 2 — 1

Repeated measure

Seq Sub1 → 1 2 3

Sub2 → 1 2 3

Sub

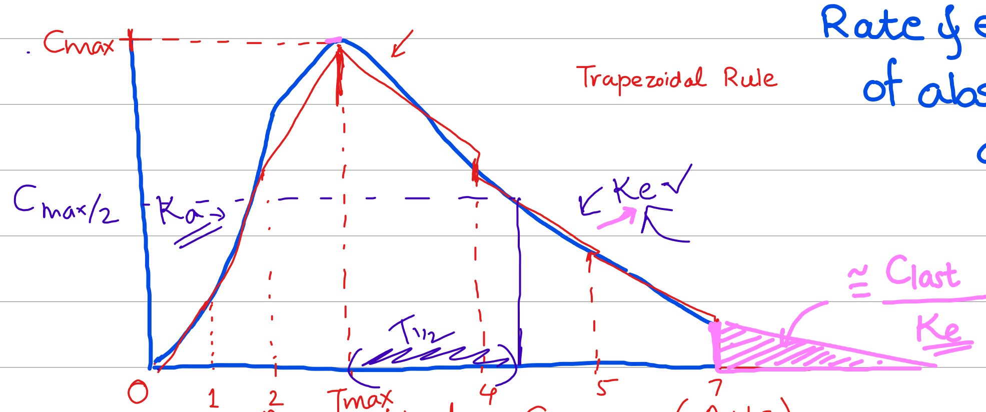
Abs : 2, 6, 9-12, 14, 16-17, 22, 33-35, 38-39, 43-45, 47, 50, 53, 56.

Pharmacokinetics Parameters

ADME

conc. blood, urine, ...

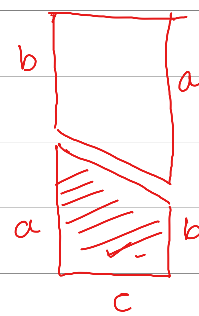
Rate & extent of absorption drug



Area Under Curve (AUC)

✓ C_{max} = max^m conc^c of drug in blood

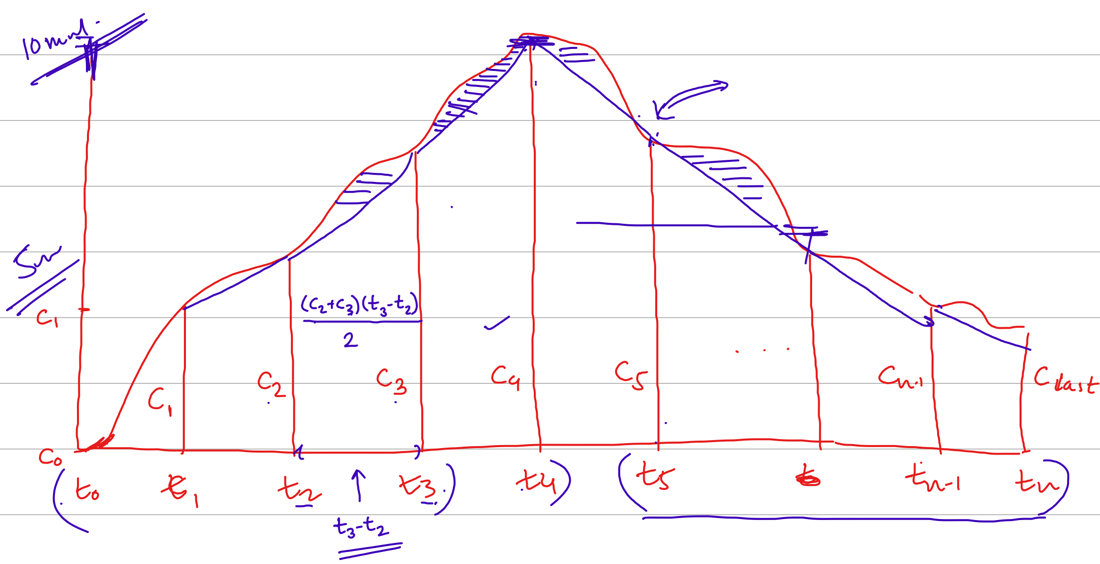
✓ T_{max} = ~~How~~ Time at which max^m conc. is achieved.



Area $\Rightarrow \frac{(a+b)c}{2}$

t_i	C_i	$\log C_i$
t_1	C_1	$\log C_1$
t_n	C_n	$\log C_n$

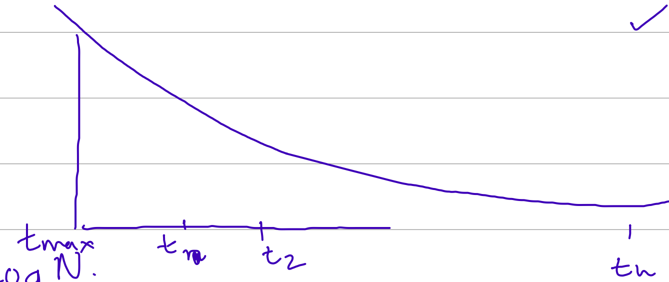
B



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

$$A_{(t-\infty)} = \frac{C_{last}}{K_e}$$

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



K_e ← Rate of excretion (sometimes by λ)

K_a - Rate of absorption

$C_i \sim$ Log N.

$$\log C_i = \alpha + \beta t_i + \varepsilon_i$$

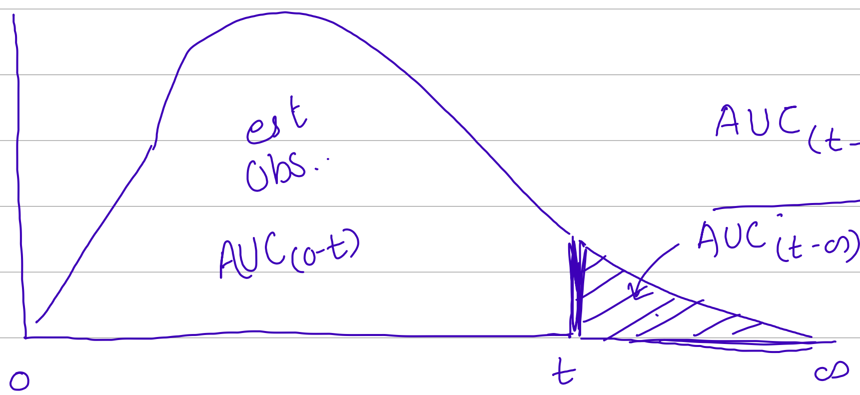
$$K_e = -2.303 \times \beta$$

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

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

$$t_{1/2} \simeq \frac{0.693}{K_e}$$

→ Treatment Duration ⇒ $6 \cdot t_{1/2}$



$$AUC_{(t-\infty)} = \frac{C_{last}}{K_e}$$

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

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

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, 55

$\cancel{y_{ijk}}$

		U_{ik}	D_{ik}	O_{ik}
y_{11}	Y_{21}	$y_{11}+y_{21}$	$\left(\frac{y_{21}-y_{11}}{2}\right)$	D_1
Y_{12}	Y_{22}	$y_{12}+y_{22}$	$\left(\frac{y_{22}-y_{12}}{2}\right)$	$-D_2$

$$\sigma_u^2 = \frac{(n_1-1)\sigma_{u_1}^2 + (n_2-1)\sigma_{u_2}^2}{n_1+n_2-2} \qquad \sigma_d^2 = \frac{(n_1-1)\sigma_{d_1}^2 + (n_2-1)\sigma_{d_2}^2}{n_1+n_2-2}$$

$$\hat{C} = \bar{U}_1 - \bar{U}_2 \qquad \hat{F} = \bar{D}_1 - \bar{D}_2 \qquad \hat{P} = \bar{O}_1 - \bar{O}_2$$

$$V(\hat{C}) = \hat{\sigma}_u^2\left(\frac{1}{n_1}+\frac{1}{n_2}\right) \qquad V(\hat{F}) \ \hat{\sigma}_d^2\left(\frac{1}{n_1}+\frac{1}{n_2}\right) \qquad V(\hat{P})$$

$$U_1 = Y_{11}+Y_{21} \qquad V(U_1) = V(2S_{i1} + \varepsilon_{i11} + \varepsilon_{i21})$$

$$= 4\sigma_s^2 + 2\sigma_e^2$$

$$\left\{ D_1 = \frac{Y_{21} - Y_{11}}{2} \right. \qquad V(D_1) = \frac{V(\varepsilon_{i21} - \varepsilon_{i11})}{4}$$

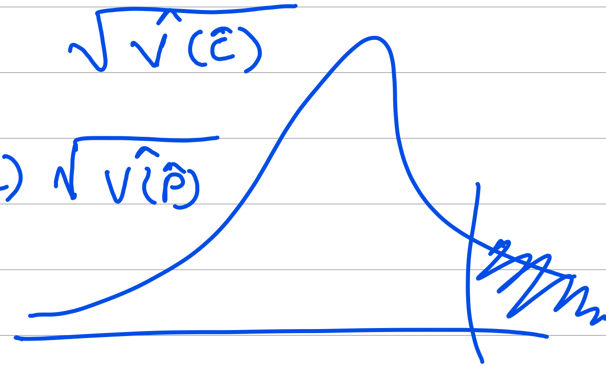
$$= \frac{2\sigma_e^2}{4} = \frac{\sigma_e^2}{2}$$

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

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

Carry over $\qquad \hat{C} \pm \sqrt{\hat{V}(\hat{C})}$

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



$2\times(1 - \text{tcdf} \quad)$

2

$P[|x| > x]$

Tdist(

$$SStotal = \sum_K \sum_j \sum_i (y_{ijK} - \bar{y}_{...})^2$$

$$= \sum_K \sum_j \sum_i (y_{ijK} - \bar{y}_{i.K} + \bar{y}_{i.K} - \bar{y}_{...})^2$$

$$= \sum_K \sum_j \sum_i (y_{ijK} - \bar{y}_{i.K})^2 + 2 \sum_K \sum_i (\bar{y}_{i.K} - \bar{y}_{...})^2$$

$$\doteq SS_{within} + SS_{Between}$$

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

$$2 \sum_K \sum_i (\bar{y}_{i.K} - \bar{y}_{...})^2 = 2 \left[\sum_K \sum_i (\bar{y}_{i.K} \right.$$

$$Y_{ijK} = \mu + S_{iK} + F_{j,K} + C_{j-1,K} + P_j + \varepsilon_{ijK}$$

sub period seq^n $\quad i = 1:n_K \quad j = 1:2 \quad K = 1:2$

1. $P_1 + P_2 = 0, \quad F_R + F_T = 0, \quad C_R + C_T = 0$
2. $\varepsilon_{ijK} \sim N(0, \sigma_e^2)$ i.i.d.
3. $S_{iK} \sim N(0, \sigma_s^2)$ i.i.d.
4. $\varepsilon_{ijK}, S_{iK}$ indep

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

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

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

$$= C_T - C_R$$

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

σ_μ^2

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

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

$$V(Y_{i12} + Y_{i22}) = V(2S_{i2} + \varepsilon_{i12} + \varepsilon_{i22}) = 4\sigma_s^2 + 2\sigma_e^2 = \underline{2(2\sigma_s^2 + \sigma_e^2)}$$

$$\hat{F} = \bar{d}_1 - \bar{d}_2 \qquad d_{iK} = \frac{1}{2}(y_{i2K} - y_{i1K})$$

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

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

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

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

Use only period-1

$$E(\bar{Y}_{.12} - \bar{Y}_{.11}) \checkmark$$

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

$$= F_T - F_R$$

y_{11}	R	T
y_{12}	T	R

$$V(Y_{i12} - Y_{i11}) = V(S_{i2} + \varepsilon_{i12} - S_{i1} - \varepsilon_{i11})$$

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

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

$$t_{stat} = \frac{\hat{F}/c}{\sqrt{V(\hat{F}/c)}} = \frac{\bar{Y}_{.12} - \bar{Y}_{.11}}{\sqrt{S_f^2\left(\frac{1}{n_1} + \frac{1}{n_2}\right)}}$$

Effect	D.f.	S.S.	MS	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	$\sum_k\sum_i \frac{Y_{i\cdot k}^2}{2} - \sum_{k=1}^{2} \frac{Y_{\cdot\cdot k}^2}{2n_k}$		MS_{Inter}/MS_{Intra}
Drug	1	$\hat{F}^2\left(\frac{2n_1 n_2}{n_1+n_2}\right)$		$MSDr/MSIntra$
Period	1	$\hat{P}^2\left(\frac{2n_1 n_2}{n_1+n_2}\right)$		$MSPe/MSIntra$
Intra	n_1+n_2-2	$\sum\sum\sum Y_{ijk}^2 - \sum_k\sum_j \frac{Y_{\cdot jk}^2}{n_k} - SS_{Inter}$		
Total	$2(n_1+n_2)-1$			

छोटा टोन्या

Chota tonya