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 # Answer to the Question # 01

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Pocock Simon Dynamic Allocation

Making Table for the 20 patients for treatment A and B

Treatment A			
	Gender (PF1)		Total
Biomarker (PF2)	Male	Female	
(+)	1	1	2
(-)	3	5	8
Total	4	6	10

Treatment B			
	Gender (PF1)		Total
Biomarker (PF2)	Male	Female	
(+)	2	2	4
(-)	3	3	6
Total	5	5	10

For weights, Wo = 2 and $W_1 = W_2 = 1$

So,

Marginal discrepancy, MD = 6

#a) Patient no. 21 male with positive biomarker:

Plug in **Male with Positive** biomarker in Treatment A:

Treatment A			
	Gender (PF1)		Total
Biomarker (PF2)	Male	Female	
(+)	2	1	3
(-)	3	5	8
Total	5	6	11

Marginal discrepancy, MD = 6

Plug in **Male with Positive** biomarker in Treatment B:

Treatment B			
	Gender (PF1)		Total
Biomarker (PF2)	Male	Female	
(+)	3	2	5
(-)	3	3	6
Total	6	5	11

Marginal discrepancy, MD = 10

Ans: **Male with Positive** biomarker will be assigned in Treatment **A**

#b) Patient no. 21 Female with positive biomarker:

Plug in **Female with Positive** biomarker in Treatment A:

Treatment A			
	Gender (PF1)		Total
Biomarker (PF2)	Male	Female	
(+)	1	2	3
(-)	3	5	8
Total	4	7	11

Marginal discrepancy, MD = 8

Plug in **Female with Positive** biomarker in Treatment B:

Treatment B			
	Gender (PF1)		Total
Biomarker (PF2)	Male	Female	
(+)	2	3	5
(-)	3	3	6
Total	5	6	11

Marginal discrepancy, MD = 8

Ans: As both MD is same **Female with Positive** biomarker will be assigned in random in Treatment **A** or **B**

#c) Patient no. 21 Male with negative biomarker:

Plug in **Male with Negative** biomarker in Treatment A:

Treatment A			
	Gender (PF1)		Total
Biomarker (PF2)	Male	Female	
(+)	1	1	2
(-)	4	5	9
Total	5	6	11

Marginal discrepancy, MD = 8

Plug in **Male with Negative** biomarker in Treatment B:

Treatment B			
	Gender (PF1)		Total
Biomarker (PF2)	Male	Female	
(+)	2	2	4
(-)	4	3	7
Total	6	5	11

Marginal discrepancy, MD = 8

Ans: As both MD is same **Male with Negative** biomarker will be assigned in random in Treatment **A** or **B**

#d) Patient no. 21 Female with negative biomarker:

Plug in **Female with Negative** biomarker in Treatment A:

Treatment A			
	Gender (PF1)		Total
Biomarker (PF2)	Male	Female	
(+)	1	1	2
(-)	3	6	9
Total	4	7	11

Marginal discrepancy, MD = 10

Plug in **Female with Negative** biomarker in Treatment B:

Treatment B			
	Gender (PF1)		Total
Biomarker (PF2)	Male	Female	
(+)	2	2	4
(-)	3	4	7
Total	5	6	11

Marginal discrepancy, MD = 6

Ans: **Female with Negative** biomarker will be assigned in Treatment B.

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 # Answer to the Question # 2

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The main objective of a phase I clinical trial is to determine the Maximum Tolerated Dose (**MTD**), Optimal Biological Dose (**OBD**) and Recommend phase II dose (**RPTD**). It also evaluates the safety, tolerability, pharmacodynamics and pharmacokinetics of an experimental drug or therapy in a small group of healthy volunteers or patients with a specific disease. In addition, defining toxicity profiles and making initial assessment of treatment efficacy are also included in phase I trials. In summary, phase I trials are the first step in the process of testing new treatments in humans, and they aim to determine the appropriate dose or range of doses to use in further clinical trials.

During a phase I trial, “dose-escalation" approach is used by the researchers. Here, participants receive increasing doses of the experimental treatment until a predetermined dose-limiting toxicity (**DLT**) is observed.

A **DLT** is a serious side effect or toxicity that is considered unacceptable or intolerable and can limit the further dose escalation.

Examples of **DLT**s include severe or life-threatening allergic reactions, organ damage, or neurological symptoms.

Maximum tolerated dose (**MTD**) is the highest dose of experimental treatment that can be given to participants without causing a DLT in a certain percentage of participants (usually around 33%).

MTD can also be defined as ≤ 1/6 of **DLT** or ≤ 2/6 of **DLT**

The MTD is often used as the recommended dose for further clinical trials to evaluate the efficacy and safety of the treatment in a larger group of patients.

In summary, the main objective of a phase I trial is to determine the safety and appropriate dosage range of an experimental treatment, and the DLT and MTD are important parameters used in the process of dose escalation and determining the appropriate dosage for further clinical trials.

 # ----------

 # Answer to the Question # 3

 # ----------

#Answer for 3 – (a) : 10000 simulations in R

 # (1) Dosage that has low toxicity probability of 0.1:

```
# Setting 10000 simulations
N <- 10000

#Probability of the toxicity
pT<- 0.10

# Put 1 if dose-escalation is happening. Put 0 otherwise.

# (Otherwise Means = MTD or no dose-escalation)

#As it is a 3+3 design cohort size =3

escalation <- function(pT)
{
  id.escal <- 1
  N.tox <- rbinom(1, 3, prob = pT)
  if(N.tox == 1) {
    tox <- rbinom(1, 3, prob = pT)
    if(tox >= 1) {
      id.escal <- 0
    }
```

```
  }
  if(N.tox > 1) { id.escal <- 0}
  return(id.escal)
}

res <- rep(NA,N)
for ( i in 1:N){
  res[i] <- escalation(pT)
}
sum(res/N)
```

 # (2) Dosage that has medium toxicity probability of 0.3:

```
# Setting 10000 simulations
N <- 10000

#Probability of the toxicity
pT<- 0.3

# Put 1 if dose-escalation is happening. Put 0 otherwise.

# (Otherwise Means = MTD or no dose-escalation)

#As it is a 3+3 design cohort size =3

escalation <- function(pT)
{
  id.escal <- 1
```

```
  N.tox <- rbinom(1, 3, prob = pT)
  if(N.tox == 1) {
    tox <- rbinom(1, 3, prob = pT)
    if(tox >= 1) {
      id.escal <- 0
    }
  }
  if(N.tox > 1) { id.escal <- 0}
  return(id.escal)
}

res <- rep(NA,N)
for ( i in 1:N){
  res[i] <- escalation(pT)
}
sum(res/N)
```

 # (3) Dosage that has high toxicity probability of 0.6:

```
# Setting 10000 simulations
N <- 10000

#Probability of the toxicity
pT<- 0.6

# Put 1 if dose-escalation is happening. Put 0 otherwise.
```

```
# (Otherwise Means = MTD or no dose-escalation)

#As it is a 3+3 design cohort size =3

escalation <- function(pT)
{
  id.escal <- 1
  N.tox <- rbinom(1, 3, prob = pT)
  if(N.tox == 1) {
    tox <- rbinom(1, 3, prob = pT)
    if(tox >= 1) {
      id.escal <- 0
    }
  }
  if(N.tox > 1) { id.escal <- 0}
  return(id.escal)
}

res <- rep(NA,N)
for ( i in 1:N){
  res[i] <- escalation(pT)
}
sum(res/N)
```

#Answer for 3 – (b): Interpretation on the simulation results

Ans: The 3+3 design is designed to determine the dose level based on the number of DLTs observed at each dose level. DLTs are defined prior to the trial and usually include certain adverse events that are considered severe enough to prevent the patient from continuing in the trial or require significant medical intervention. If no DLTs are observed in a cohort, the dose is typically escalated, while if one or more DLTs are observed, the dose is typically de-escalated. And the goal of the 3+3 design is to identify the MTD, which is the highest dose level that is associated with an acceptable rate of DLTs.

So, based on my simulation it can be said that:

If Toxicity is Low - The study may need to increase the dose levels to identify the maximum tolerated dose more rapidly.

If Toxicity is High - The study may consider reducing the dose levels or altering the dose escalation scheme.

Though it is true that, it is rigid; not flexible and inefficient, in my opinion, it is a good design to identify DLT and MTD.

#Answer for 3 – (c): Bonus Question: Doing part (a) based on statistical theory:

Ans: Yes, I think I can solve part (a) based on statistical theory.

Theoretical dose escalation probability formula is:

$$p^0 (1-p)^3 + 3p (1-p)^5$$

 # (1) Dosage that has low toxicity probability of 0.1

That means, p = 0.1

Then, Theoretical dose escalation probability = 0.906147 or 90.614%

 # (2) Dosage that has medium toxicity probability of 0.3:

That means, p = 0.3

Then, Theoretical dose escalation probability = 0.494263 or 49.4263%

 # (3) Dosage that has high toxicity probability of 0.6:

That means, p = 0.6

Then, Theoretical dose escalation probability = 0.082432 or 8.2432%