Medical Statistics (MATH38071) Solutions Exercise Sheet 8

(Analysis with Treatment Protocol Deviations)

1. Tabulated below are data from a randomised controlled trial comparing Inpatient and Outpatient treatment for patients with anorexia nervosa Outpatient Care.

	Randomization			
	In patient (T)		**Outpatient (C)**	
Recovered	**Received Inpatient**	**Received Outpatient**	**Received Inpatient**	**Received Outpatient**
N	60	10	40	25
Y	140	90	60	175
Total	200	100	100	200

(i) Calculate the point estimates of the a) Intention-to-treat, b) Per-Protocol and c) As-Treated treatment effect.

Solution

	Inpatient P_T	**Outpatient** P_C	**Treatment Effect** $P_T - P_C$
Intention-to-treat	**70/300**	**65/300**	**0.017**
Per-Protocol	**60/200**	**25/200**	**0.175**
As-Treated	**100/300**	**35/300**	**0.217**

Assume that there are three latent classes of patients in a randomised trial (A) patients who will comply with the allocated treatment, (B) patients who will always have inpatient care and (C) patients who will always have outpatient care.

(ii) By considering those patients allocated to inpatient care, estimate the proportion of patients who will always receive outpatient care.

Solution

One third (100/300) of the patients in the inpatient group had out-patients care. Assuming that they would have out-patient care if randomized to out-patient care, an estimate the proportion that will always have outpatient care is 1/3.

(iii) By considering those patients allocated to outpatient care estimate the proportion that will always receive inpatient care.

Solution

One third (100/300) of the patients in the out-patient care had in-patients care. Assuming that they would have been in-patient care , if randomized to in-patient care. An estimate of the proportion that will always have outpatient care is 1/3.

(iv) Hence estimate the proportion of subjects who will comply with random allocation.

Solution

Assuming that the proportions of the three types of patient is the same in both arms, from (ii) and (iii) it follows that 2/3 of patients will always the same treatment irrespective of randomisation. Therefore the proportion of patients who will comply with the allocated treatment is 1/3.

(v) Estimate the Compliance Average Causal Effect (CACE) from the Intention-To-Treat (ITT) effect.

Solution

From the notes the Compliance Average Causal Effect estimate of the treatment effect $\hat{\tau} = \hat{\tau}_{ITT} / \theta_A$ where $\hat{\tau}_{ITT}$ is the ITT estimate and θ_A is the patients who will comply with the random allocation. Hence $\hat{\tau} = 0.017/(1/3) = 0.051$

(vi) What assumptions are made in obtaining the CACE estimate?

Solution

Three assumptions are made:

1) There are no defyers, that is patients who always receive the opposite of the allocated treatment.
2) The proportion and characteristics of the three latent classes compliers, always control, always new treatment is the same in both arms, which is justified by randomization.
3) Randomization only effects outcome through treatment.

(vii) Comment on the difference between the CACE point estimate with the point estimates for Intention-to-treat, Per-Protocol and As-Treated estimates of the treatment effect calculated in part (i).

Solution

What is noticeable is the treatment effect for the As Treated analysis (0.217) and the Per-protocol analysis (0.175) are much larger than the CACE estimate of treatment effect (0.051). The intention to treat estimate is smaller (0.017). Whilst the non-compliance in this study was very much larger than what might be normally be expected, this illustrates why an ITT analysis is preferable to an As Treated or a Per-protocol analysis as it is biased towards the null whereas the latter may give a greatly exaggerated estimate where there is substantial non-compliance.

2. Consider a randomized controlled trial. Suppose the patient population can be divided into three latent sub-groups as follows:

- *Compliers*: patients who will comply to the allocated treatment,
- *Always control treatmen*t: patients who will receive control treatment regardless of allocation,
- *Always new treatment*: patients who will receive the new treatment regardless of allocation.

Assuming that the proportion and characteristics of *compliers*, *always control treatment*, *always new treatment* is the same in both arms and that randomization can only affect the outcome through the receipt of treatment, show that an *as-treated* estimate of the treatment effect may be biased either towards or away from the null hypothesis of no treatment effect.

Solution

The solution similar to that for Per-Protocol Estimate that was given in the notes.

Model of expected mean outcome of each treatment and latent sub-group

	Type	**Control Group**	**New Treatment Group**	**Proportion In Latent Class**
As Randomized	A	μ	$\mu+\tau$	$\theta_A\left(=1-\theta_B-\theta_C\right)$
Always Control	B	$\mu+\gamma_B$	$\mu+\gamma_B$	θ_B
Always New Treatment	C	$\mu+\gamma_C+\tau$	$\mu+\gamma_C+\tau$	θ_C

$$\tau_{AT}=\left(\frac{\theta_A\left(\mu+\tau\right)+2\theta_C\left(\mu+\gamma_C+\tau\right)}{\theta_A+2\theta_C}\right)-\left(\frac{\theta_A\mu+2\theta_B\left(\mu+\gamma_B\right)}{\theta_A+2\theta_B}\right)$$

$$=\left(\frac{\left(\theta_A+2\theta_C\right)\mu+2\theta_C\gamma_C+\left(\theta_A+2\theta_C\right)\tau}{\theta_A+2\theta_C}\right)-\left(\frac{\left(\theta_A+2\theta_B\right)\mu+2\theta_B\gamma_B}{\theta_A+2\theta_B}\right)$$

$$=\tau+\mu+\left(\frac{2\theta_C\gamma_C}{\theta_A+2\theta_C}\right)-\mu-\left(\frac{2\theta_B\gamma_B}{\theta_A+2\theta_B}\right)$$

$$=\tau+\left(\frac{2\theta_C}{\theta_A+2\theta_C}\right)\gamma_C-\left(\frac{2\theta_B}{\theta_A+2\theta_B}\right)\gamma_B$$

The values of γ_C and γ_B can be positive or negative so that the second and third terms can be either positive or negative. Hence, the bias can be away from or towards the null hypothesis.

3. Consider a parallel group randomized controlled superiority trial that compares a new treatment with a standard treatment. Suppose the outcome measure is continuous with its standard deviation equal to σ. Suppose the causal effect of treatment is τ and the proportion of patients expected to comply with randomization is π.

(i) Write down an expression for the intention-to-treat estimate of the treatment effect.

Solution

From the notes the ITT treatment effect, $\tau_{ITT}=\pi.\tau$

(ii) The formula for sample size per group for a superiority trial is $n = \frac{2\sigma^2}{\delta^2}\left(z_{\alpha/2} + z_{\beta}\right)^2$ where δ the intention-to-treat treatment effect is. Suggest a modified formula for sample size based on the causal effect of treatment τ and that the proportion of patients expected to comply with randomization is π.

Solution

Given that the ITT effect $\tau_{ITT} = \pi.\tau$ where τ is the causal effect (compliance average causal effect) one just replaces τ by $\pi.\tau$ in the above formula giving the sample size per group $n_{nc} = \frac{2\sigma^2}{\pi^2\tau^2}\left(z_{\alpha/2} + z_{\beta}\right)^2$

(iii) Assuming that all patients comply with treatment, the sample size per group for a trial has been estimated to be 256. It is thought that 20% of patients recruited to the trial will not comply with random allocation. Determine a revised sample size per group that takes account of this non-compliance.

Solution

If 20% of patients are expected not to comply, the proportion that do comply is $\pi = 1 - 0.2 = 0.8$

Suppose N is the sample size Given that the $N_{nc} = \frac{N}{\pi^2}$ it follows that sample size per group taking account of non-compliance is $n_{nc} = \frac{256}{0.8^2} = 400$.