8. Analysis with Treatment Protocol Deviations

Sometime patients in a randomised controlled trial do not receive the treatment allocated. After consenting they or their care provider may change their mind, perhaps due to the change in the patient's health. Patients may decide not to take the tablets. A patient may start a treatment but then default or change to another before receiving an adequate dose. In these situations the patient may be said to be non-compliant or non-adherent. These changes from the randomly allocated treatment are sometimes referred to as *Treatment Protocol Deviations.*

If patients do not adhere to their randomly allocated treatment, should they be included in the statistical analyses, and if so how?

Analysis Strategies Where There is Non-Compliance

- ***Intention-To-Treat analysis (ITT):*** Patients are analysed according to the group to which they were randomized, irrespective of whether they received the intended intervention. Also called ***As-Randomized***
- ***Per-Protocol (PP):*** Patients are analysed within the intervention group to which they were randomized after exclusion of non-compliant patients.
- ***As-Treated (AT):*** Patients are analysed according to the treatment they actually received irrespective of the random allocation.

Table 8.1 Comparison of *intention-to-treat* with *as treated* and *per-protocol* analysis

Survival at 2 years	Randomization			
	Medical treatment		Surgery	
	Received medicine [1]	Switch to surgery [2]	Received Surgery [3]	Switched to medicine [4]
Died	27 (8.36%)	2 (4%)	15 (4.07%)	6 (23%)
Alive	296	48	354	20
Total	323	50	369	26

Two-year mortality in the coronary bypass surgery trial published by the European Coronary Study Group (1979) from E Marubini M.G. Valsecchi Analysing survival Data from Clinical Trials and Observational Studies, p22 Wiley 1996.

Table 8.2 Summary of Mortality Rates for each Analysis Method

Analysis	Medical P_M	Surgical P_S	Treat. Effect $P_M - P_S$
Intention-to-treat	$\frac{29}{373} = 7.7\%$	$\frac{21}{395} = 5.32\%$	2.45%
Per-protocol	$\frac{27}{323} = 8.36\%$	$\frac{15}{369} = 4.07\%$	4.29%
As-treated	$\frac{27+6}{323+26} = 9.46\%$	$\frac{17}{419} = 4.06\%$	5.4%

Table 8.3 Summary of Inferential Analysis using a z-test for Proportions

Analysis	Treat. Effect $P_M - P_S$	95% c.i.	p-value	Signif. In a 5% level test
Intention-to-treat	2.45%	-1.05% to 5.96%	0.168	Not Sig.
Per-protocol	4.29%	0.66% to 7.92%	0.018	Sig
As-treated	5.40%	1.79% to 9.00%	0.003	Sig

In this trial the patients that changed from medical treatment to surgery appear to be different from those patients who changed from surgery to medical treatment. Only 2/50 (4%) of those that switched from medicine to surgery died, whereas 6/26 (23%) of those that switched from surgery to medicine died, a difference in mortality of 19%. This suggests that the prognosis of these two patient sub-groups were very different.

If we assume that the composition of the two groups of patients randomised to either surgery or medical treatment are the same, there will be a group of patient in [1] who have a poor prognosis like those in [4] of table 8.1.

8.1 Comparison of ITT, PP And AT Analyses

When testing $H_0: \tau = 0$ vs $H_1: \tau \neq 0$, where there is non-compliance the *Intention-to-Treat* estimate $\hat{\tau}_{ITT}$ is biased toward H_o whereas the *Per-Protocol* estimate $\hat{\tau}_{PP}$ and the *As-Treated* estimate $\hat{\tau}_{AT}$ may be biased either towards or away from H_o.

A simple mathematical model can be constructed to illustrate the difference between the three estimates of treatment effect. We suppose that the patient population can be divided into three sub-groups as follows:

Group A - who comply with the allocated treatment (Compliers – Always as randomised)
Group B - who will always receive control treatment regardless of allocation (Always Control Treatment)
Group C- who will receive the new treatment regardless of allocation. (Always New Treatment)
It is assumed that there are no **defyers**, that is patients who will always receive the opposite of the treatment to which they are randomly allocated.

As patients enter the trial the sub-group membership of a patient is not known or "latent". Patients in each of the three compliance sub-groups or "latent classes" are likely to have a different prognosis. Considering example 7.1 if surgery was the New Treatment and medical was the Control, group B is patient that would always receive

medical treatment. We saw that those patients appear to have a worse prognosis.

As the patients are randomly allocated the expected proportions of patients in each of the three latent classes is the same in each arm of the trial. For simplicity of presentation it will be assumed that the treatment effect compared to the control treatment is τ, in all three "latent classes". The quantity τ is the causal effect of treatment, sometimes called by the *Compliance Average Causal Effect (CACE)*, which is the average treatment effect in patients that comply with the New treatment.

Table 8.4 Model of expected mean outcome for each treatment and latent sub-group

CACE effect

	Latent Class	Control Treatment Group	New Treatment Group	Probability in Latent Class
As Randomized	**A**	μ	$\mu + \tau$	θ_A
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 $(=1 - \theta_A - \theta_B)$

Assumptions of Model

- No *defyers*, that is patients who always receive the opposite of the allocated treatment.
- Proportion and characteristics of the three latent classes *compliers*, *always control*, *always new treatment* is the same in both arms. This is justified by randomization.
- Randomization only effects outcome through treatment.

From the table of expected means the *Intention-to-Treat* estimate is

$$\tau_{ITT} = \left[\theta_A(\mu+\tau)+\theta_B(\mu+\gamma_B)+\theta_C(\mu+\gamma_C+\tau)\right] - \left[\theta_A\mu+\theta_B(\mu+\gamma_B)+\theta_C(\mu+\gamma_C+\tau)\right] = \theta_A\tau$$

as second and third terms in each bracket cancel.

Hence $|\tau_{ITT}| \le \tau$ which means τ_{ITT} is biased towards zero if θ_A <1 i.e. if some patients do not comply with treatment. Hence $E[\hat{\tau}_{ITT}] \le \tau$

The *Per-Protocol* estimate is

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

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

$$= \tau+\mu+\left[\frac{\theta_C\gamma_C}{\theta_A+\theta_C}\right]-\mu-\left[\frac{\theta_B\gamma_B}{\theta_A+\theta_B}\right]$$

$$= \tau+\left[\frac{\theta_C\gamma_C}{1-\theta_B-\theta_C+\theta_C}\right]-\left[\frac{\theta_B\gamma_B}{1-\theta_B-\theta_C+\theta_B}\right]$$

$$= \tau+\left[\frac{\theta_C\gamma_C}{1-\theta_B}\right]-\left[\frac{\theta_B\gamma_B}{1-\theta_C}\right]$$

τ_{PP} is biased by terms involving γ_B and γ_C. Since γ_B and γ_C can be either positive or negative $\hat{\tau}_{PP}$ may be biased either towards or away from zero.

A similar expression can be derived for the As-Treated estimate that also shows that it can also be biased towards or away from zero depending on the magnitude of γ_B and γ_C.

Advantages of Intention-to-Treat

The Intention-to-Treat analysis is always biased towards zero so that the efficacy of the treatment is being under-estimated. In a superiority trial, use of *intention-to-treat* biases the statistical analysis towards the null hypothesis. If one rejects the null hypothesis H_o: τ =0 based on an *intention-to-treat* analysis, one can feel confident that the treatment effect is larger in patients that actually take the treatment. An analysis based on *intention-to-treat* is therefore said to be conservative. This is not true for *per-protocol* and *as-treated* analyses as both can be biased either towards or away from the null hypothesis.

Another advantage of intention-to treat analysis is that randomization clearly defines the groups being compared so there is no ambiguity as to how the patients should be included in the analysis. In contrast, the groups being compared in per-protocol or as-treated analyses may be less well defined. Whether a particular patient completes treatment is often difficult to obtain. Even if one is able to collect reliable data on the treatment, the researchers needs to agree how many tablets or therapy sessions a patient has to receive before they can be considered to have complied with treatment, which is an issue for which there may be no consensus. For this reason an ITT analysis may therefore be easier to implement than Per-protocol or As-treatment analyses.

It is important that all patients are followed-up, not just those that receive treatment, for ITT analysis to be carried out.

8.2 Efficacy and Effectiveness

Efficacy and *Effectiveness* are two terms used to describe the ability to produce an effect such cure a specific illness. In clinical trials a distinction is drawn between efficacy (also known as ideal use) and effectiveness (also known as typical use). We have already seen that where there is non-compliance, Intention-to-treat underestimates the efficacy of a treatment.

Intention to Treat Analyses and Effectiveness

Researchers may not be just interested in whether treatment works in patients who receive a treatment. They may want to know the overall effect of offering a treatment. This is particularly true for health policy makers. For example in a trial of exercise for the treatment of back-pain some patients may not comply. If only a small proportion of patient take the treatment, the average benefit of offering the treatment may be small, even if it is beneficial in patients that comply. It may be important to know the effectiveness, which is the effect taking account of non-compliance, as there are likely to be "costs" associated with offering the treatment to patients that do not comply. It can be argued that the intention-to-treat (ITT) analysis gives an estimate of treatment effect taking account of non-compliance. For this reason ITT is sometimes said to give an estimate of the effectiveness of treatments. This interpretation of ITT assumes that the proportion of patients that comply in the trial is the same as in normal care, which may not be true.

8.3 Estimating Efficacy and the CACE estimate

Suppose instead the researcher is interested in efficacy. Provided the assumptions below table 7.5 hold, the compliance average causal effect (CACE) estimate can be obtained.

From above the ITT estimate $\tau_{ITT} = \tau\theta_A$. Hence, the *Compliance Average Causal Effect* is

$$\tau = \tau_{ITT}/\theta_A .$$

$\hat{\tau}_{ITT} = \bar{y}_T - \bar{y}_C$ for continuous data and

$\hat{\tau}_{ITT} = p_T - p_C$ for binary data.

One needs an estimator of θ_A, the proportion of patients who comply with randomization. This can be obtained as follows:

- Suppose the observed proportions who receive the new treatment in the treatment and control groups are respectively q_T and q_C.
- Considering the control group, $q_c = \hat{\theta}_C$
- Considering the new treatment group, $q_T = \hat{\theta}_A + \hat{\theta}_C$
- Hence θ_A can be estimated by $\hat{\theta}_A = q_T - q_C$.

Hence the *Compliance Average Causal Effect* can be estimated by

$$\hat{\tau} = \frac{\hat{\tau}_{ITT}}{q_T - q_C}.$$

It should be noted that this estimate assumes that there are only two treatments that patients can switch between. This method does not work where one is comparing two active treatments and some patients default to a third option such as no treatment.

Ex 8.2 For the bypass surgery example above the Intention-to-Treat estimate of the treatment was 2.45% , 4.29% for a Per-Protocol analysis and 5.40% for an As-treated analysis. Estimate the Compliance Average Causal Effect , τ.

$q_T =$ (proportion randomised to surgery that get surgery) $= \frac{369}{(369+26)} = 0.934$ (from Surgery Arm Data)

$q_C =$ (proportion randomised to medical treat. that get surgery) $= \frac{50}{323+50} = 0.134$ (from Medical Treatment Arm)

Hence $\hat{\tau} =$

$$= \frac{\hat{E}_{ITT}}{q_T - q_C} = \frac{0.0245}{0.934 - 0.134} = 0.031$$

The causal effect of treatment is 3.1% , which is smaller than the Per-Protocol (4.3%) and As-Treat estimates (5.4%). Under the assumption we have made, one can see that the Per-Protocol and As-Treat estimates are both biased away from the null.

The test that the compliance average causal effect (CACE) is zero is equivalence to the test that the intention to treat effect (ITT) is zero, that is $H_0 : \tau = 0$ is equivalent to $H_0 : \tau_{ITT} = 0$.

Intention-to-Treat and Equivalence and Non-inferiority Trials

Application of the intention-to-treat (ITT) analysis in an equivalence trial has problems, as it is biased towards the alternative hypothesis of no difference between treatments. An ITT analysis may therefore increase the probability of accepting the alternative hypothesis. Good compliance with treatment is therefore very important in both equivalence and non-inferiority trials.