A1

> (i)   In the context of a randomised controlled trial (RCT), explain what is meant by the term double-blind.

This is method to reduce bias in a randomised controlled trial, where neither the study participant nor the experimenter knows which of two treatments the participant is receiving [2 mark]

> (ii)   Give two advantages of a RCT being double-blind?

It is advantageous for a trial to be double blind as knowledge of treatment allocation may influence the behaviour of the patient, the treating health professional or the assessor of outcome. For example if the patient know which treatment they are receiving it may motivate them to default from treatment or seek alternative treatments. If the treating health professional know the allocation it may influence choice of secondary treatments. If the outcome assessor is aware of treatment, allocation there judgement may be bias. For example if may effect a patients self assessment if they know that they have received a placebo or standard treatment.

[2 marks]

> (iii)   Give an example of treatment that cannot be evaluated in be double-blind clinical trial.

A clinical trial of surgery cannot be double blind because the surgeon must be aware of which treatment has been allocated.

[2 marks]

[Total 6 marks]

A2

Tabulated below are data from randomised controlled trial comparing a surgical and medical treatment for elderly stroke patients .

	Surgery		Medical	
Survival at 3 years	*Received Surgery*	*Received Medical*	*Received Surgery*	*Received Medical*
No	*15*	*15*	*4*	*26*
Yes	*105*	*45*	*26*	*124*
Total	*120*	*60*	*30*	*150*

(i) *Calculate the point estimates of the treatment effect of surgery compared to medical treatment measured by the proportion surviving at 3 years for (a) Intention-To-Treat, (b) Per-Protocol and (c) As-Treated analyses.*

(a) *Intention-To-Treat* treatment effect $=(105+45)/(120+60)-(26+124)/(30+150)=0.0$
(b) *Per-Protocol* treatment effect $=105/120-124/150=0.048$
(c) *As-Treated* treatment effect$=(105+26)/(150)-(45+124)/210=0.\ 0.069$

[4 marks]

(ii) *Briefly explain why an Intention-To-Treat analysis is usually preferable to a Per-protocol and As-Treated analyses.*

Use of *intention-to-treat* biases the statistical analysis towards showing no difference between two treatments. In a superiority trial this is a bias towards the null hypothesis. If we reject the null hypothesis $H_o:\delta=0$ based on an *intention-to-treat* analysis, one can feel confident that the treatment effect is larger in patients that took the treatment. An intention-to-treat analysis is therefore conservative. In contrast *per-protocol* and *as-treated* analyses may be biased either away from or towards the null hypothesis. An *Intention-to-treat* analysis may also be thought of as the pragmatic estimate as it estimates the effect of treatment taking account of non-compliance.

[3 marks]
[total 7 marks]

A3

A randomised controlled crossover trial is used to assess whether thyroxin treatment is effective in patients with symptoms of hypothyroidism. Patients were randomised to either thyroxin then placebo(TP) or placebo then thyroxin (PT). The table below summarizes the sample mean and standard deviation (s.d.) of the free thyroxin (pmol/l) in the blood.

Sequence	period 1		period 2		period 2 – period 1		n
	mean	*s.d.*	*mean*	*s.d.*	*mean*	*s.d*	
TP	*18.4*	6.4	*18.3*	7.2	-0.1	3.5	20
PT	*16.1*	6.3	*19.2*	6.9	3.1	3.4	20

(i)   Using the summary data from just period 1 test the null hypothesis that thyroxin does not affect free thyroxin levels stating necessary assumptions.

A test of the comparison thyroxin against placebo using just period 1 data is a two-sample t-test of $H_o: \mu_1 = \mu_2$ where μ_1 and μ_2 are the population means for the sequences TP and PT in the first period.

Assuming outcome measure Y is normally distributed, equal within group standard deviations and independence, the two sample t-test is defined by

$$T = \frac{\bar{y}_1 - \bar{y}_2}{s.e.(\bar{y}_1 - \bar{y}_2)}$$ where $\bar{y}_1, \bar{y}_2$ are the sample means for the sequences TP and PT in the first

period, $s.e.(\bar{y}_1 - \bar{y}_2) = s\sqrt{1/n_1 + 1/n_2}$, $s = \sqrt{\dfrac{(n_1 - 1).s_1^2 + (n_2 - 1).s_2^2}{n_1 + n_2 - 2}}$ and $v = n_1 + n_2 - 2$

For period 1 $s = \sqrt{\dfrac{(n_1 - 1).s_1^2 + (n_2 - 1).s_2^2}{n_1 + n_2 - 2}} = \sqrt{\dfrac{6.4^2 + 6.3^2}{2}} = 6.349$

$$s.e.(\bar{y}_1 - \bar{y}_2) = s\sqrt{1/n_1 + 1/n_2} = 6.349 \times \sqrt{\frac{1}{20} + \frac{1}{20}} = 2.074$$

Hence $T = \dfrac{18.4 - 16.1}{2.0741} = 1.109$

Degrees of freedom, $v = n_1 + n_2 - 2 = 38$. For a test size α=0.05 from tables $t_{\alpha/2}(38) \cong 2.04$.

Hence the null hypothesis of no treatment effect would not be rejected.

[4 marks]

(ii)   Using the summary data for the difference between period 2 and period 1 test the null hypothesis that thyroxin does not affect free thyroxin levels.

In a AB-BA crossover trial, treatment effect can be estimated by

$\hat{\delta} = \dfrac{\bar{d}_{PT} - \bar{d}_{TP}}{2}$. The hypothesis $H_0: \delta = 0$ vs. $H_1: \delta \neq 0$ can be tested using a two-sample t-test of the means of the differences. The test statistic T_d is defined as

$$T_d = \frac{\bar{d}_{PT} - \bar{d}_{TP}}{\hat{SE}\left[\bar{d}_{PT} - \bar{d}_{TP}\right]} \quad \text{where } \hat{SE}\left[\bar{d}_{TP} - \bar{d}_{PT}\right] = s_d\sqrt{\frac{1}{n_{TP}} + \frac{1}{n_{PT}}} \quad \text{and}$$

$$s_d = \sqrt{\frac{\left(n_{PT} - 1\right)s^2_{d_{PT}} + \left(n_{TP} - 1\right)s^2_{d_{TP}}}{n_{PT} + n_{TP} - 2}}.$$

$$s_d = \sqrt{\frac{\left(n_{PT} - 1\right)s^2_{d_{PT}} + \left(n_{TP} - 1\right)s^2_{d_{TP}}}{n_{PT} + n_{TP} - 2}} = 3.450$$

$$\hat{SE}\left[\bar{d}_{TP} - \bar{d}_{PT}\right] = s_d\sqrt{\frac{1}{n_{TP}} + \frac{1}{n_{PT}}} = 3.450 \times \sqrt{\frac{1}{10}} = 1.091$$

Hence

$$T_d = \frac{\bar{d}_{PT} - \bar{d}_{TP}}{\hat{SE}\left[\bar{d}_{PT} - \bar{d}_{TP}\right]} = \frac{3.1 - (-0.1)}{1.091} = 2.932$$

For a test size α=0.05 from tables $t_{\alpha/2}(38) \cong 2.04$ Hence the null hypothesis would be rejected.
[5 marks]

(iii)   Outline the advantages and disadvantages of a cross-over design as compared to parallel group design.

Advantage
- Within patient control means that variation between patients is removed hence sample size may be substantially smaller as seen above.

Disadvantages
- Only applicable to certain types of condition such as stable or chronic diseases. Unsuitable were the condition make resolve

- More complicated to organize.

- If a patient withdraws during period 2 mean due to the condition having resolved the will be no data for the second period and so the data from the first period cannot be included in the statistical analysis.
 [5 marks]

[Total 14 marks]

A4

(i) Explain the difference between a fixed effect and a random effect meta-analysis.
Suppose that there are k studies and that the treatment effect for the ith study is θ_i. There are
two approaches to obtaining an overall estimate of the treatment effect.

The Fixed-Effect Analysis assumes that the studies all estimate the same overall effect of

treatment say θ and that the departure of $\hat{\theta}_i$ from θ is due to sampling variation. *The*

Random-Effects Analysis assumes that the studies are sampled from a larger population of

studies and that θ_i is a random variable.

[4 marks]

(iii) In the context of a meta-analysis, what is a funnel plot?

A funnel plot is scatter diagram in which the total sample size of each trial is plotted against
the treatment effect for that study as illustrated

[Possibly Illustration]
 [2 marks]

(iv) When carrying out a meta-analysis why might one draw a funnel plot?

When studies estimate the same size treatment effect, the distribution of points should
resemble an inverted funnel shape with a widening in the spread of effect sizes as sample size
decreases. This is because the standard error of the effect size is approximately proportional to
the inverse of the square root of the sample size. If there is publication bias some studies with
an effect size closer to the null may not be published. This will cause the funnel plot to be
asymmetric. A funnel plot is therefore graphical technique for detecting possible publication
bias.

[3 marks]

 [total 9 marks]

Q5
Describe three designs for sampling a population to gather data on the relationship between
an exposure and disease. Give two factors which should influence the choice between these
designs, given that there is a fixed budget for the study.

 (i) Choose two samples of subjects known to be exposed and unexposed respectively. Then
determine their disease status
(ii) Choose two samples of subjects known to have the disease and to be free of disease
respectively. Then determine their exposure status.
(iii) Choose a single sample – at random perhaps – from the population and then determine
their exposure and disease status.

The choice will depend on availability of information – (i) and (ii) are only possible if there is pre-existing information on exposure and disease status respectively.

The choice should also depend on statistical efficiency. For example, if the aim is to estimate the odds ratio then, depending on prevalence of exposure and prevalence of disease in the population, one design may give a more efficient estimate than the others.

Q6.

Consider the problem of estimating $\theta_j = \lambda_{1j}/\lambda_{0j}$ where λ_{1j} and λ_{0j} are rate of liver cancer in age-group j of an exposed male workforce and of the male population of the UK respectively, j=1,...k, under the assumption that $\theta_j = \theta$ for all j and when the rates λ_{0j} are already known.

Data on the observed number of cancers, b_j and corresponding man-years at risk, T_j in each age-group of the workforce are to be collected.

(i) Show that the maximum likelihood estimator of θ is $\dfrac{\sum b_j}{\sum \lambda_{0j} T_j}$

(ii) Estimate θ from the following data.

Age-group	W'force:m-years	W-force: LC deaths	UK: rate of LC per 10,000 p-years
1	1000	1	5
2	2000	4	15
3	1500	7	30

(i) It is usual to assume that the RV B_j has a Poisson distribution with mean $\lambda_{1j}T_j$. Since $\lambda_{1j} = \theta\lambda_{0j}$, we assume Poisson ($\theta\lambda_{0j}T_j$). Hence the likelihood (L) of the observed data is

$$\prod_j \frac{\exp(-\theta\lambda_{0j}T_j)(\theta\lambda_{0j}T_j)^{b_j}}{b_j!} \text{ and } \log L = -\theta\sum\lambda_{0j}T_j + \sum b_j \ln(\theta\lambda_{0j}T_j) + terms\ not\ involving\ \theta.$$

$$\Rightarrow \frac{dLL}{d\theta} = -\sum\lambda_{0j}T_j + \sum\frac{b_j}{\theta}.$$

Setting $\dfrac{dLL}{d\theta} = 0$ and solving for θ gives $\hat{\theta}_{MLE} = \dfrac{\sum b_j}{\sum\lambda_{0j}T_j}$.

[Bookwork]

(ii)

Age-Group	W'force: p-years T_j	W'force: LC deaths	UK: rate of LC per 10,000 p-years, λ_{0j}	$\lambda_{0j}T_j$
1	1000	1	5	5*1000/10000=0.5
2	2000	4	15	15*2000/10000=3.0
3	1500	7	30	30*1500/10000=4.5
Total		**12**		**8.0**

From Table, $\hat{\theta} = \dfrac{12}{8} = 1.5$.

08/05/20066:31 PM

B7

In a parallel group equivalence trial a new treatment T is compared with a control treatment C on a continuous outcome measure Y. Let $\bar{y}_T$, $\bar{y}_C$, μ_T and μ_C be the sample and population means of Y for each treatment, n_T and n_C be the sample sizes, and s be the common within-group sample standard deviation of Y. Define $\tau = \mu_T - \mu_C$ as the treatment effect.

(i) Explain why a significance test of the hypothesis $H_0 : \tau = 0$ vs $H_1 : \tau \neq 0$ would be an *inappropriate in an equivalence trial.*
[3marks]

In order to demonstrate an effect we need to reject a null hypothesis so that we can accept an alternate hypothesis. Hence to demonstrate that a new treatment is equivalent, we need to define a null hypothesis that the treatment is not equivalent which can then be rejected in favour of an alternative hypothesis that the treatment is equivalent.

Suppose that the null hypothesis that $H_0 : |\mu_T - \mu_T| \geq \delta_E$ against the alternative hypothesis $H_1 : |\mu_T - \mu_T| < \delta_E$ is rejected, when the (1-2α) confidence interval, given by $\bar{y}_T - \bar{y}_C \pm z_\alpha \lambda s$ with $\lambda = \sqrt{1/n_T + 1/n_C}$, is within the interval (-δ_E, +δ_E).

(ii) *Show that*
$$Pr[Reject\ H_0| \tau] = \Phi\left((\delta_E - \tau)/\lambda s - z_\alpha\right) - \Phi\left(-(\delta_E + \tau)/\lambda s + z_\alpha\right)\ where\ \Phi\ is\ the$$
cumulative distribution function of the standard Normal distribution.
[6 marks]

$Pr[Reject\ H_0|\tau] = Pr[\bar{y}_T - \bar{y}_C + z_\alpha \lambda s < \delta_E | \tau]$ - $Pr[\bar{y}_T - \bar{y}_C - z_\alpha \lambda s < -\delta_E | \tau]$

Assuming normality

$Pr[\bar{y}_T - \bar{y}_C + z_\alpha \lambda s < \delta_E | \tau] = Pr[\dfrac{\bar{y}_T - \bar{y}_C}{\lambda s} < \dfrac{\delta_E}{\lambda s} - z_\alpha | \tau] = \Phi\left[\dfrac{\delta_E}{\lambda s} - z_\alpha - \dfrac{\tau}{\lambda s}\right]$

$Pr[\bar{y}_T - \bar{y}_C - z_\alpha \lambda s < -\delta_E | \tau] = Pr[\dfrac{\bar{y}_T - \bar{y}_C}{\lambda s} < -\dfrac{\delta_E}{\lambda s} + z_\alpha | \tau] = \Phi\left[-\dfrac{(\delta_E + \tau)}{\lambda s} + z_\alpha\right]$

$Pr[Reject\ H_0|\tau] = Pr[\bar{y}_T - \bar{y}_C + z_\alpha \lambda s < \delta_E | \tau]$ - $Pr[\bar{y}_T - \bar{y}_C - z_\alpha \lambda s < -\delta_E | \tau] = \Phi\left[\dfrac{\delta_E}{\lambda s} - z_\alpha - \dfrac{\tau}{\lambda s}\right]$ -

$\Phi\left[-\dfrac{(\delta_E + \tau)}{\lambda s} + z_\alpha\right]$ as required.
[Bookwork]

(iii) *Show that Pr[Reject H$_0$| τ] has a maximum under H$_0$ when $\tau = -\delta_E$ or $\tau = \delta_E$. Hence show that this procedure has a type I error $\leq \alpha$.*

We can find the maximum of this by differentiation w.r.t. τ.

$$\frac{d}{d\tau}\left(1-\beta(\alpha,\tau)\right) = -\frac{1}{s\lambda}\phi\left((\delta_E-\tau)/s\lambda - z_\alpha\right) + \frac{1}{s\lambda}\phi\left(-(\delta_E+\tau)/s\lambda + z_\alpha\right)$$ where ϕ is the

standard normal density.

Since ϕ is symmetric about 0, it follows that $\phi\left(-(\delta_E+\tau)/s\lambda + z_\alpha\right) = \phi\left((\delta_E+\tau)/s\lambda - z_\alpha\right)$.

Hence $\frac{d}{d\tau}(1-\beta(\alpha,\tau))$ is zero when $\phi\left((\delta_E-\tau)/s\lambda - z_\alpha\right) = \phi\left((\delta_E+\tau)/s\lambda - z_\alpha\right)$

which occurs if and only if $\tau = 0$.

Since Pr(Reject $H_0|\tau$)tend to zero as τ tends to $\pm\infty$, this is a maximum.

The Type 1 error rate is the probability of rejecting the null when it hold, that is when $\tau \leq -\delta_E$ or $\tau \geq \delta_E$.

Since Pr(Reject $H_0|\tau$) will be monotone increasing for $\tau < 0$ and monotone decreasing for $\tau > 0$ it follows that the maximum of the Type I error occurs at the boundary values $\tau = -\delta_E$ and $\tau = \delta_E$,

When $\tau = \delta_E$
Pr(Reject $H_0|\tau$)=$1-\beta(\alpha,\delta_E) = \Phi\left((\delta_E/s\lambda - z_\alpha) - \delta_E/s\lambda\right) - \Phi\left((-\delta_E/s\lambda + z_\alpha) - \delta_E/s\lambda\right)$
$= \Phi(-z_\alpha) - \Phi(-2\delta_E/s\lambda + z_\alpha) = \alpha - \Phi(z_\alpha - 2\delta_E/s\lambda) \leq \alpha$.
Similarly if $\tau = -\delta_E$

Hence under the null hypothesis H_0: $|\tau| > \delta_E$, Pr(Reject $H_0|\tau$)$\leq\alpha$

[8 marks] [Bookwork]

An equivalence trial is carried out to test whether a new cheaper generic drug with is as

effective as an existing proprietary drug for controlling blood pressure. Twenty-five patients

receive each treatment. The table below summarizes the systolic blood for each treatment

group. A difference of 5 mmHg was considered to be clinically important.

	Treatment Group					
	Generic Drug			*Proprietary Drug*		
	Mean	*S.D.*	*N*	*Mean*	*S.D.*	*N*
Systolic Blood Pressure (mmHg)	135.5	14.7	25	136.1	15.1	25

(iv)   The 90% confidence interval for the mean difference between the Proprietary Drug and the Generic Drug is (-7.9 mmHg, 9.1 mmHg). Comment on the results.

Since a difference of 5 mmHg was considered to be clinically important this suggest a range of equivalence (-5 mmHg,5 mmHg). The 90% confidence interval is not included within the range of equivalence (-5 mmHg,5 mmHg). Hence one cannot reject the null hypothesis that the two drugs differ. Nevertheless the mean difference between the two treatment is small (0.4 mmHg). This suggest that the study was under powered.

[4 marks]

(v)   Explain why treatment compliance is particularly important in an equivalence trial.

If patients do not comply with treatment or switch treatments in a clinical trial the outcome for the treatment groups will tend to closer together than if patients complied with treatment. In a superiority trial this is a bias against rejecting the null hypothesis, whilst in an equivalence trial this is a bias towards the alternative hypothesis. Hence poor compliance in an equivalence trial can undermine the conclusion that two treatments are equivalent.

[4 marks]

B8 *A randomised controlled trial is planned to compare a treatment (A) with the current standard therapy (B). For an outcome measure Y let $\bar{y}_A$, $\bar{y}_B$, μ_A, μ_B the sample and population means of Y for each treatment, and s be the common within-group sample standard deviation of Y. Assume that the null hypothesis of no treatment effect $H_0 : \mu_A = \mu_B$ will be tested by the statistic $T = \dfrac{\bar{y}_A - \bar{y}_B}{s\lambda}$, with $\lambda = \sqrt{1/n_A + 1/n_B}$ where n_A, n_B are the number of subjects allocated to each treatment.*

(i)   Write down an expression for the power of the test for a two-tailed alternative hypothesis, stating the assumptions you make.

Assuming *n* is sufficiently large such that a normal approximation to the central and non-central t-distribution is adequate,

$$Power = 1 - \beta(\alpha, \tau) = \left(1 - \Phi\left(z_{\alpha/2} - \frac{\tau}{\sigma\lambda}\right)\right) + \Phi\left(-z_{\alpha/2} - \frac{\tau}{\sigma\lambda}\right) \quad [1]$$

where $\lambda = \sqrt{1/n_A + 1/n_B}$ and Φ is the cumulative distribution function of the standardised normal distribution, N(0,1).

[Bookwork]

[5 marks]

(ii)   Assuming that patients are allocated in the ratio of 1:k with $n_B = k.n_A$ show that the total sample size required to give a power (1-β) for a two-tailed α size test is

$$n = \frac{(k+1)^2}{k} \frac{\sigma^2}{\tau^2}\left(z_{\alpha/2} + z_\beta\right)^2$$

.

The second term in equation [1] is negligible, therefore

$$Power = 1 - \beta(\alpha, \tau) \cong 1 - \Phi\left(z_{\alpha/2} - \frac{\tau}{\sigma\lambda}\right)$$

Since $\Phi^{-1}(\beta) = -z_\beta$ it follows that $-z_\beta = z_{\alpha/2} - \frac{\tau}{\sigma\lambda}$

giving $\dfrac{\tau}{\sigma\lambda} = z_{\alpha/2} + z_\beta$.

If $n_B = k.n_A$, then $\lambda = \sqrt{1/n_A + 1/kn_A} = \sqrt{(k+1)/kn_A}$

Therefore $\dfrac{\tau}{\sigma}\sqrt{\dfrac{kn_a}{(k+1)}} = z_{\alpha/2} + z_\beta$. Rearrangement gives

$$\frac{kn_a}{(k+1)} = \frac{\sigma^2}{\tau^2}\left(z_{\alpha/2} + z_\beta\right)^2$$

and $n_a = \left(\dfrac{k+1}{k}\right)\dfrac{\sigma^2}{\tau^2}\left(z_{\alpha/2} + z_\beta\right)^2$

Hence the total sample size $n = n_a + kn_a = \dfrac{(k+1)^2}{k}\dfrac{\sigma^2}{\tau^2}\left(z_{\alpha/2} + z_\beta\right)^2$

[8 marks]

(iii)   Show that the minimum sample size is obtained by using an equal allocation ratio.

[5 marks]

To find the minimum differentiate with respect to k.

$$\frac{dn}{dk} \propto \frac{d}{dk}\left(k + 2 + \frac{1}{k}\right) = 1 - \frac{1}{k^2}$$

Equating derivative to zero gives

$\left(k^2 - 1\right) = 0$ gives k=1

Since the second derivative is positive, this must be a minimum. k=1 corresponds to an equal allocation ratio.

(iv)   In a randomised controlled trial it is planned to randomised 240 patients into two treatments. The pooled within group standard deviation is estimated to be 12 units. Estimate the power of a study to detect a treatment effect of 5 units for two-tailed 0.05 size test with an allocation ratio of 1:2.

[3 marks]

From above $Power \cong 1 - \Phi\left(z_{\alpha/2} - \dfrac{\tau}{\sigma\lambda}\right)$

σ=12, α=0.05 , $z_{\alpha/2}$=1.96 τ=5,

Hence $Power \cong 1 - \Phi\left(1.96 - \dfrac{5}{12\sqrt{\dfrac{1}{80} + \dfrac{1}{160}}}\right) = 1 - \Phi(-1.08) \cong 0.86$

(v) Describe how you could randomly allocate patients to treatments with an allocation ratio of 1:2 using block randomisation.

08/05/20066:31 PM

The simplest way of allocating patients with an allocation ratio of 1:2 would be to use a block size of 3. With this block size there are 3 blocks (1) AAB (2) ABA and (3) BAA. A sequence of random integers between 1 and 3 could then be used to compile a list. If the random numbers 1,3,2,3 are chosen the treatment sequence for 12 patients would be

$$AAB\ BAA\ ABA\ \ BAA.$$

[4 marks]

[25 marks]

Q9. *An investigator wishes to estimate the effect of hormone replacement therapy (HRT) on incidence of heart disease. Assume the true ratio of the incidence rate in users of the therapy versus that in comparable unexposed people is* θ_H.

The investigator estimates θ_H *by* t_H, *the ratio of the observed cumulative incidence rate in a group of users versus a group of never-users. However the groups are not comparable since proportions* p_1 *and* p_0 *of the users and never-users were smokers; smoking multiplies the incidence of heart disease by a factor* θ_S.

(i) Show that $t_E = \dfrac{\theta_H(1-p_1+\theta_S p_1)}{(1-p_0+\theta_S p_0)}$.

(i) Suppose the rate of HD in non-smokers, non-HRT users ($\bar{S},\bar{H}$) is r. It follows that the rates in the other groups are:

Sub-group	$\bar{S},\bar{H}$	$\bar{S},H$	$S,\bar{H}$	S,H
Rate	R	$r\theta_H$	$r\theta_S$	$r\theta_S\theta_H$

The overall rate in a group of size n of whom a proportion p are in sub-gp 1 with disease rate π_1 and a proportion 1-p have rate π_2 is the weighted average $p\pi_1 +(1-p) \pi_2$. It follows that the overall rate in the user group is

$$p_1 r\theta_S\theta_H +(1-p_1)r\theta_H = r\theta_H (p_1\theta_S+1-p_1).$$

In the never-user group it is

$$p_0 r\theta_S +(1-p_0)r \quad = r(p_0\theta_S+1-p_0).$$

Hence the ratio of these, $t_E = \dfrac{r\theta_H(\theta_S p_1 +1- p_1)}{r(\theta_S p_0 +1- p_0)} = \dfrac{\theta_H(1- p_1 +\theta_S p_1)}{(1- p_0 +\theta_S p_0)}$.

BOOK WORK

[6 marks]

(ii) Suppose that θ_H= 1.5, θ_S= 5, p_1=0.2 *and* p_0=0.7. *Calculate* t_E *and comment on your result in relation to the effect of HRT.*

(ii) $t_E = \dfrac{1.5(0.8+5*0.2)}{(0.3+5*0.7)} = \dfrac{2.7}{3.8} = 0.71$. This result appears to show that HRT reduces the incidence of heart disease. However it is biased since the true value is 1.5, ie HRT increases the rate.

[3 marks]

(iii) Show that when $\theta_H > 1$ and $\theta_S > 1$, a necessary condition for $t_E < 1$ is that $p_0 > p_1\theta_H$.

(iii).
$$t_E < 1 \Leftrightarrow \theta_H(1 - p_1 + \theta_S p_1) < (1 - p_0 + \theta_S p_0)$$
$$\Leftrightarrow \theta_H - 1 + \theta_H p_1(\theta_S - 1) < p_0(\theta_S - 1)$$
$$\Leftrightarrow \theta_H - 1 < (\theta_S - 1)(p_0 - \theta_H p_1)$$

Since $\theta_H - 1 > 0$ and $\theta_S - 1 > 0$ the inequality is satisfied only if $\quad p_0 - p_1\theta_H > 0 \Rightarrow p_0 > p_1\theta_H$.

BOOK WORK

[4 marks]

(iv) In a different study to address the same question, the investigator collects data on 4 variables: regular alcohol use (yes/no), diabetic status (Yes/No), Body Mass Index (BMI, a continuous measure) and HRT use (ever/never) from 1017 women. The incidence of heart attacks over 5 years is also recorded and recorded as ≥1 or 0. The following logistic regression analyses using STATA software are produced.

A.

```
Logit estimates                                Number of obs   =        1007
                                               LR chi2(4)      =       34.43
                                               Prob > chi2     =      0.0000
Log likelihood = -354.58                       Pseudo R2       =      0.0463
------------------------------------------------------------------------------
      attack |    Coef.    Std. Err.      z     P>|z|     [95% Conf. Interval]
---------+-------------------------------------------------------------------
         HRT |    .0244     0.1979      0.12    0.902     -0.3634      0.4123
     alcohol |   -.2141     0.2402     -0.89    0.373     -0.6848      0.2566
    diabetes |   1.1681     0.2258      5.17    0.000      0.7254      1.6107
         bmi |   0.0331     0.0156      2.12    0.034      0.0025      0.0675
       _cons |  -3.0529     0.5200     -5.87    0.000     -4.0722     -2.0336
------------------------------------------------------------------------------
```

B

```
Logit estimates                                Number of obs   =        1007
                                               LR chi2(1)      =        0.00
                                               Prob > chi2     =      0.9932
Log likelihood = -375.07                       Pseudo R2       =      0.0000


------------------------------------------------------------------------------
      attack |    Coef.    Std. Err.      z     P>|z|     [95% Conf. Interval]
---------+-------------------------------------------------------------------
         HRT |   -.4104     0.1923     -2.13    0.033     -0.7873     -0.0335
       _cons |  -1.9827     0.1366    -14.52    0.000     -2.2504     -1.7150
------------------------------------------------------------------------------
```

(iv) *Calculate the odds ratios for alcohol, BMI and diabetes and use the results of the tests to interpret information about the relationships between each of these factors and the risk of heart attacks.*

The ORs for alcohol, diabetes and BMI are [exp(-0.2141 etc] 0.81, 3.22, 1.034.

The OR for alcohol is 0.81, suggesting that regular alcohol use decreases the odds of a heart attack. However a test of H_0: γ (odds ratio) =1 gives p=0.373 (2-sided), so we cannot reject H_0 on the basis of this test (and 5% sig level).

The OR for diabetes is 3.22 suggesting that people with diabetes have treble the odds of a heart attack. Also a test of H_0: γ =1 gives p < 0.001 (2-sided) suggesting that we can reject H_0 with 5% sig level.

The OR for BMI is 1.034 suggesting higher BMI increase risk. The test of H_0: γ =1 gives p=0.034 (2-sided), suggesting we can reject H_0 (5% level).
[6 marks]

(v)   What is the odds ratio comparing two people with BMI measurements that are 5 units apart?

The OR for BMI refers to an increase of one unit. For an increase of 5 units, the OR is $\exp(5*0.0331)= 1.18 = (1.034)^5$.
[2marks]

(vi)Calculate the odds ratios for HRT from Analysis A and Analysis B. Why might the results for HRT be different? Which one is likely to be the better indicator of the effect of HRT and why?
The odds ratios for HRT from A and B are 1.025 and 0.66 respectively. In analysis A, the estimate of HRT effect is corrected/adjusted for potential confounding by alcohol, diabetes, BMI. This is not the case in Analysis B. The estimate in B may therefore be biased. The estimate for A is preferable for this reason. Of course the estimate in A is not corrected for other potential confounders eg smoking so there may still be some bias.
[4 marks]

[total 25 marks]