

1. (a) In the context of diagnostic testing, define the terms *prevalence*, *sensitivity*, *specificity* and *positive predictive value*. Use Bayes' theorem to show how positive predictive value is related to the other three quantities. [8 marks]
- (b) In certain transplant procedures, patients with a high viral load of Cytomegalovirus (measured in units of  $\log_{10}$  genomes/mL) are thought to have an increased risk of severe disease following transplantation. To investigate this, a random sample of 49 transplant patients was taken and the following data recorded.

Viral load	Severe disease		Total
	Yes	No	
$\leq 4.5$	8	28	36
$> 4.5$	7	6	13
Total	15	34	49

- (i) Calculate the sensitivity and specificity of 'viral load greater than 4.5' as a predictor of severe disease.
- (ii) Calculate the positive predictive value assuming the patients to be a random sample from the population to be screened.
- (iii) Recalculate the positive predictive value if the prevalence in the population to be screened is 10%.
- (iv) Comment briefly on the values obtained in (i), (ii), (iii) above. [7 marks]
- (c) Describe what a Receiver Operating Characteristic (ROC) curve is. Explain how an ROC curve might be useful in improving the design of the screening test described in part (b) above, and say what further data would need to be collected. [5 marks]

2. (a) Briefly outline the main features of *cohort studies* and *case-control studies*. Give one advantage of each and one disadvantage of each.

Define the terms *relative risk* and *odds ratio* with respect to a population. Under what conditions are they approximately equal? [9 marks]

- (b) A case-control study was carried out among 220 Nigerian women to investigate whether sexual characteristics are associated with subsequent development of cervical cancer. A questionnaire was administered to 47 cases and 173 controls, and the women were classified according to whether they first had sexual intercourse before or after 15 years of age. The resulting data were as follows.

Age of first sexual intercourse	Cases	Controls
$\leq 15$ years	36	78
$> 15$ years	11	95

Calculate the odds ratio and its 95% confidence interval, and interpret your results.

Is there evidence of an association between age of first sexual intercourse and development of cervical cancer? [8 marks]

- (c) It is proposed to carry out a study to investigate the same question in South Africa, where the incidence rate of cervical cancer is around 30 cases per 100 000 women per year. Would a case-control study or a cohort study be your preferred design, and why? [3 marks]

3. In a study of ovarian cancer, 20 patients were each randomly assigned to one of two treatment groups. The times (in months) from diagnosis until death were as follows.

Group A: 4, 5, 9, 11, 14, 16\*, 21, 24\*, 24\*, 24\*

Group B: 12, 12, 12\*, 14\*, 16, 19, 24\*, 24\*, 24\*, 24\*

(\* denotes a censored observation).

(a) Calculate the Kaplan-Meier estimate of the survivor function for each of the two treatment groups separately and display your results graphically. Comment on the relationship between the two graphs.

[10 marks]

(b) Test the hypothesis that there is no difference between the treatments given to these two groups of patients, and interpret your result.

Comment briefly on the Kaplan-Meier graphs of part (a) and on the design of the study in the light of the conclusion of your hypothesis test.

[10 marks]

4. (a) Outline the main features of a Bayesian analysis, including definitions of the terms *prior distribution*, *likelihood* and *posterior distribution*.

Describe two possible sources of prior information in the context of a Bayesian analysis of a clinical trial comparing two treatments, and define the term *conjugate prior*.

[8 marks]

- (b) In a clinical trial to compare a particular treatment with no treatment with respect to one-year mortality, it is decided to analyse the results in a Bayesian framework.

For no treatment, previous evidence regarding the probability  $\theta_N$  of death within one year can be summarised by regarding  $\theta_N$  as following a Beta distribution with parameters  $\alpha_N = 80$ ,  $\beta_N = 320$ . For the treatment under study, expert belief about the probability  $\theta_T$  of death within one year can be summarised by regarding  $\theta_T$  as following a Beta distribution with parameters  $\alpha_T = 50$ ,  $\beta_T = 280$ .

Express your current beliefs about the log of the odds ratio for one-year mortality of the treatment under study compared to no treatment, and calculate a 95% credibility interval for this quantity. Hence give a 95% credibility interval for the odds ratio for one-year mortality of the treatment compared to no treatment, and interpret your result.

[Hint: If  $\theta_N \sim \text{Beta}(\alpha_N, \beta_N)$  and  $\theta_T \sim \text{Beta}(\alpha_T, \beta_T)$ , then  $\log_e \left( \frac{\theta_T / (1 - \theta_T)}{\theta_N / (1 - \theta_N)} \right)$  is approximately Normally distributed with mean  $\mu$  and variance  $\sigma^2$  given by

$$\mu = \log_e \left( \frac{(\alpha_T - 0.5)(\beta_N - 0.5)}{(\alpha_N - 0.5)(\beta_T - 0.5)} \right) \quad \sigma^2 = \frac{1}{\alpha_N} + \frac{1}{\beta_N} + \frac{1}{\alpha_T} + \frac{1}{\beta_T} \quad ]$$

[6 marks]

- (c) The trial was carried out and the results reported as follows. Of 180 patients randomised to the treatment, 21 had died within one year, whereas of 160 patients randomised to receive no treatment, 24 had died.

Use the above data to calculate a sample estimate of the odds ratio for one-year mortality of the treatment compared to no treatment.

From the above data, a posterior 95% credibility interval for the odds ratio for one-year mortality of the treatment compared to no treatment was computed to be (0.51, 0.98). Interpret this interval, and comment on the relationship between the prior beliefs, the sample data, and the posterior beliefs in this trial.

[6 marks]

5. The table below shows the results of 8 randomised trials comparing two surgical treatments for severe angina. The response considered was myocardial infarction (MI), whether fatal or not, within one year of treatment.

Trial	Treatment A		Treatment B	
	MI ( $a_i$ )	No MI ( $b_i$ )	MI ( $c_i$ )	No MI ( $d_i$ )
1	29	484	43	498
2	31	470	34	476
3	33	161	24	174
4	18	159	10	172
5	6	70	6	70
6	1	69	5	67
7	2	64	6	62
8	7	57	8	55

- (a) The Mantel-Haenszel pooled log odds ratio across all 8 trials,  $\hat{y}_p$ , is given by

$$\hat{y}_p = \frac{\sum_{i=1}^8 w_i \hat{y}_i}{\sum_{i=1}^8 w_i}$$

where  $\hat{y}_i$  is the estimated log odds ratio for trial  $i$ , and  $w_i = 1/\text{Var}(\hat{y}_i)$ .

$$\left[ \text{Note: } \hat{y}_i = \log_e \left[ \frac{a_i d_i}{b_i c_i} \right] \text{ and } \text{Var}(\hat{y}_i) = \frac{1}{a_i} + \frac{1}{b_i} + \frac{1}{c_i} + \frac{1}{d_i} \right]$$

Calculate the value of  $\hat{y}_p$  and interpret your computed value. [8 marks]

- (b) The value of the statistic for testing for heterogeneity of treatment effects between the 8 trials was found to be

$$Q = \sum_{i=1}^8 w_i (\hat{y}_p - \hat{y}_i)^2 = 10.82$$

Test whether there is evidence of heterogeneity in the results of the trials. Interpret your result, and comment on whether it is appropriate to combine the results into a single pooled estimate of treatment effect.

[4 marks]

- (c) Explain what is meant by *publication bias*. Use a graphical method to investigate whether there is evidence of publication bias in the above data.

[8 marks]

6. (a) Describe briefly the four different phases into which trials are conventionally divided in pharmaceutical development. [7 marks]
- (b) In a randomised trial of two treatments, where the outcome measure may be assumed to follow a Normal distribution, the number of patients required may be determined using the formula

$$n = \frac{2\sigma^2}{d^2} \left( \Phi^{-1}(1 - \beta) + \Phi^{-1} \left( 1 - \frac{\alpha}{2} \right) \right)$$

Explain what each of the terms  $n$ ,  $\sigma$ ,  $d$ ,  $\alpha$  and  $\beta$  represents. [5 marks]

- (c) In planning a study to compare two treatments for anorexia nervosa, it is proposed to assign patients randomly to two groups and record each patient's weight gain in kilograms after three months. From previous experience it is expected that the standard deviation of weight gain will be 4 kg for each group. The investigator feels that a difference in mean weight gain between the two groups of 3 kg would be of clinical importance, and wishes to test for such a difference with a power of 90% at the 5% significance level. How many patients will be required for the study?

The investigator believes that the difference in mean weight gain between the two groups is likely to be around 5 kg. With the same significance level and power as before, calculate the number of patients required to detect such a difference.

Comment on the relationship between the two sample sizes you have computed.

[8 marks]

7. (a) Describe briefly the Cox regression model for survival data, explaining what is meant by the *proportional hazards* assumption. [4 marks]
- (b) In a study of the effects of psychiatric intervention on cancer survival, 68 patients with malignant melanoma were each randomly assigned to either receive the treatment or not, and then followed up for 10 years. After 10 years, 11 of the 34 patients in the control group had died, compared with 9 of the 34 patients in the treatment group. A Cox proportional hazards model was fitted to the survival time data, with the following variables.

$$\text{Treatment } (X_1) = \begin{cases} 0 & \text{Control group} \\ 1 & \text{Treatment group} \end{cases}$$

$$\text{Sex } (X_2) = \begin{cases} 0 & \text{Female} \\ 1 & \text{Male} \end{cases}$$

Thickness ( $X_3$ ) : Tumour thickness at the thickest point, in millimetres

The results of fitting the model were as follows.

Variable	$\hat{\beta}$	$p$ -value
Treatment ( $X_1$ )	-1.055	0.05
Sex ( $X_2$ )	1.955	0.002
Thickness ( $X_3$ )	0.852	<0.001

- (i) Write down the fitted model. [2 marks]
- (ii) For each covariate in turn, interpret the given  $p$ -value and calculate and interpret the relative hazard. What would you conclude about the effectiveness of the treatment? [8 marks]
- (iv) Define the ‘risk score’ for this model.  
Calculate the value of the risk score for Patient A, a male with tumour thickness 0.6 mm who is assigned to the treatment group, and also for Patient B, a female with tumour thickness 1.7 mm who is also assigned to the treatment group. Which of these two patients is at greater risk? [4 marks]
- (v) Give two reasons why multiple linear regression would not be appropriate for the above data. [2 marks]