1. In a randomised trial in women with breast cancer, ten patients were treated with standard chemotherapy and ten patients were given a new form of chemotherapy. Their survival times, measured in months from randomisation, were as follows:

Standard: 7*, 10*, 10*, 30, 37, 38, 41, 42, 44, 57

New: 11, 12, 20*, 80, 85, 95, 100*, 100*, 100*, 100*

* denotes a censored observation.

(a) Calculate the Kaplan-Meier estimate of the survivor function for each of the two treatment groups separately. Display the results graphically. [10 MARKS]

(b) Test the null hypothesis that there is no difference between the treatments given to these patients, and interpret your results. [8 MARKS]

(c) Would a proportional hazards model be appropriate for these data? Give a reason for your answer. [2 MARKS]

2.(a) Describe four fundamental principles which should be applied when considering whether to introduce a screening program for a particular disease. [4 MARKS]

(b) The score from the Child Behaviour Checklist hyperactivity (CBCH) scale has been proposed as a method of screening for attention deficit disorder with hyperactivity (ADDH). To assess this approach, the following data were collected on 467 patients:

	ADDH	
	Yes	No
CBCH score 0-4	1	43
CBCH score 5-9	3	104
CBCH score 10-14	30	127
CBCH score 15-20	41	40
Indeterminate results	15	63

(i) Ignoring the patients with indeterminate test results, and taking higher CBCH scores to indicate ADDH, calculate the sensitivity and specificity of the test for each cut-off level of CBCH. [6 MARKS]

(ii) Plot the Receiver Operating Characteristic (ROC) curve. [4 MARKS]

(iii) Consider the following scenario: Each child diagnosed positive on CBCH is to be treated. The treatment is effective, relatively cheap and has few serious side effects. Untreated hyperactive children have a high chance of developing further behavioural problems. Which cut-off level do you consider would give the best screening test? Give reasons for your answer. [2 MARKS]

(iv) The indeterminate test results arise because it is not always possible to complete all items of the CBCH scale during the assessment of the child. Using the cut-off level selected in (b)(iii) above, consider how the indeterminate test results should be treated and recalculate the values for sensitivity and specificity. Comment on your findings. [4 MARKS]

3. A clinical trial has been undertaken to compare a new treatment with a control treatment with respect to one-year mortality. The researchers decided before the trial began that they wished to analyse the results in a Bayesian framework. It can be assumed that the probability of death at one year on the control group, θ_c, follows a Beta distribution with parameters α_c and β_c. The parameters α_c and β_c can be written in terms of $E(\theta_c)$ and $V(\theta_c)$ in the following way:

$$\alpha_c = \frac{-[E(\theta_c)]^3 + [E(\theta_c)]^2 - E(\theta_c)V(\theta_c)}{V(\theta_c)}$$

$$\beta_c = \frac{[E(\theta_c)]^3 - 2[E(\theta_c)]^2 + E(\theta_c) - V(\theta_c) + E(\theta_c)V(\theta_c)}{V(\theta_c)}$$

It can also be assumed that the probability of death at one year on the new treatment, θ_n, follows a Beta distribution with parameters α_n and β_n.

(a) Summarising previous evidence suggests that for the control treatment, the estimate of one-year mortality, assumed to be normally distributed, is around 30% with approximate 95% certainty that it is no less than 25% and no more than 35%. The new treatment is believed to reduce mortality to around 10%, with corresponding 95% certainty that it is no less than 5% and no more than 15%.

(i) Assuming estimate $E(\theta_c)$, $V(\theta_c)$, $E(\theta_n)$ and $V(\theta_n)$. Hence estimate α_c, β_c, α_n and β_n.

[5 MARKS]

(ii) Express your current beliefs about the log of the odds ratio for one-year mortality of the new treatment compared to the control treatment, and calculate a 95% credibility interval for this quantity.

[Hint: If $\theta \sim$ Beta (α,β), $\log(\theta/(1-\theta))$ is approximately $N\left(\log\left(\frac{\alpha-0.5}{\beta-0.5}\right), \quad \frac{1}{\alpha}+\frac{1}{\beta}\right)$]

[5 MARKS]

(b) The trial was conducted and the results were reported as follows: out of 250 patients randomised to the new treatment 50 had died by one year, whilst on the control treatment 60 out of 250 randomised patients had died. Estimate the distribution of the log of the posterior odds ratio and calculate a 95% credibility interval using the prior information described above. Comment on the posterior compared to the prior beliefs.

[Hint: if there are r_c deaths out of n_c patients on the control treatment, and r_n deaths out of n_n on the new treatment, the log of the posterior odds ratio is approximately Normally distributed with mean μ and variance σ^2 given by

$$\mu = \log\left[\frac{(\alpha_n + r_n - 0.5)(\beta_c + n_c - r_c - 0.5)}{(\alpha_c + r_c - 0.5)(\beta_n + n_n - r_n - 0.5)}\right]$$

$$\sigma^2 = \frac{1}{\alpha_c + r_c} + \frac{1}{\beta_c + n_c - r_c} + \frac{1}{\alpha_n + r_n} + \frac{1}{\beta_n + n_n - r_n} \quad]$$

[10 MARKS]

4. Given below are extracts from a published systematic review: Crowley P. Prophylactic corticosteroids for preterm birth (Cochrane Review). In: The Cochrane Library, Issue 4, 2000. Oxford: Update Software.

Give answers to the following questions using evidence from the article when appropriate.

(a) How would you interpret the pooled odds ratio and its confidence interval for the mortality outcome in this review?

[3 MARKS]

(b) Explain in general terms what is meant in a meta-analysis of RCTs by statistical heterogeneity.

[2 MARKS]

How would you interpret the results from the test for heterogeneity in this analysis?

[2 MARKS]

(c) Using graphical methods examine whether there is any evidence of publication bias in this analysis. [Hint: to ease the calculations, use the results for the odds ratio and its 95% confidence interval given in the final column of the figure but work with the log(odds ratio)]

[13 MARKS]

Prophylactic corticosteroids for preterm birth

Crowley P

Background: Respiratory distress syndrome is a serious complication of prematurity causing significant immediate and long-term mortality and morbidity.

Objectives: The objective of this review was to assess the effects of corticosteroids administered to pregnant women to accelerate fetal lung maturity prior to preterm delivery.

Search strategy: The Cochrane Pregnancy and Childbirth Group trials register was searched.

Selection criteria: Randomised trials of corticosteroid drugs capable of crossing the placenta compared with placebo or no treatment in women expected to deliver preterm as a result of either spontaneous preterm labour, prelabour rupture of the membranes preterm, or elective preterm delivery.

Data collection and analysis: Eligibility and trial quality were assessed by one reviewer.

Main results: Eighteen trials including data on over 3700 babies were included. Antenatal administration of 24 milligrams of betamethasone, of 24 milligrams of dexamethasone, or two grams of hydrocortisone to women expected to give birth preterm was associated with a significant reduction in mortality (odds ratio 0.60, 95% confidence interval 0.47 to 0.75) and respiratory distress syndrome (odds ratio 0.53, 95% confidence interval 0.44 to 0.63).

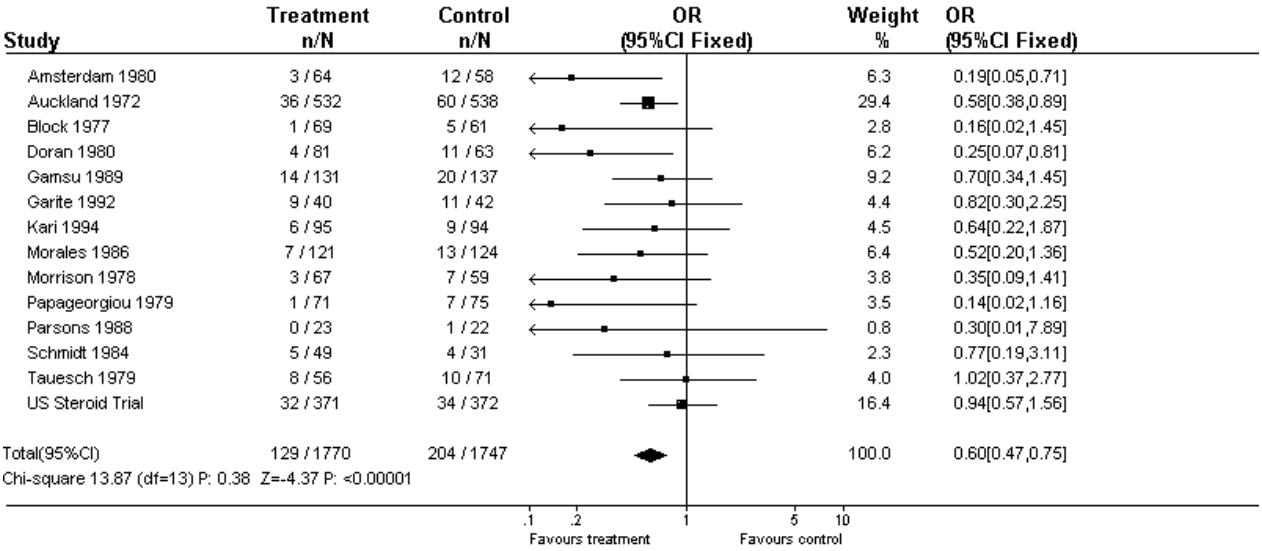
These benefits extended to a broad range of gestational ages and were not limited by gender or race.

Reviewers' conclusions: Corticosteroids given prior to preterm birth (as a result of either preterm labour or elective preterm delivery) are effective in preventing respiratory distress syndrome and neonatal mortality.

Question 4 continued overleaf

Q4 contd

Comparison: 01 Corticosteroids versus placebo or no treatment
Outcome: 01 Neonatal death



5. In a randomised trial, two drugs were compared for their ability to prolong time to an attack in 100 patients with asthma. The intention was to follow patients up for a maximum of three weeks. Eighty patients suffered an asthma attack, at times ranging from 10 to 18 days (median 13 days). Of the remaining 20 patients, 6 did not complete two weeks' follow-up. The covariate age was also measured on each patient.

(a) Define what is meant by a censored observation in survival analysis. [2 MARKS]

(b) A Cox proportional hazards model was fit to the data. Coding for the variables was as follows:

Treatment (X_1): 0 drug A Age (X_2): in years
1 drug B

The results are given in the following table:

Variable	$\hat{\beta}$	s.e.$(\hat{\beta})$	p-value
Treatment (X_1)	-0.43	0.22	0.045
Age (X_2)	0.02	0.01	0.029

(i) Write down the fitted model. [2 MARKS]

(ii) Interpret the results as fully as possible. [6 MARKS]

(c) The outcome variable described above was re-coded as a binary variable `attack before 14 days'. The six patients who did not complete 2 weeks' follow-up were excluded from the analysis. A logistic regression model was then fit to the data with age as a covariate. The results are given in the following table:

Variable	$\hat{\beta}$	s.e.$(\hat{\beta})$	p-value
Intercept	-0.19	0.80	0.81
Treatment (X_1)	-1.89	0.45	0.0001
Age (X_2)	0.04	0.02	0.057

(i) Write down the fitted model. [2 MARKS]

(ii) Interpret the results for treatment and age as fully as possible. [6 MARKS]

(d) Would you have expected the results in (b) and (c) to be different or similar? Justify your answer briefly. [2 MARKS]

6. The table below shows data from a study of men working in 18 asbestos factories during the period 1933-1937 inclusive. Mortality from lung cancer was of particular interest. The observed number of deaths from lung cancer amongst the factory workers in that period was 84.

Age group	Number of male asbestos workers	Annual death rate per 100000 for lung cancer in men in England and Wales
25-29	160	2
30-34	620	3
35-39	1096	9
40-44	1403	22
45-49	1496	54
50-54	1427	119
55-59	1192	216
60-64	887	346
65-69	540	508
70-74	322	651

(a) Calculate the standardised mortality ratio (SMR) for the factories based on these data. Interpret your findings.

[7 MARKS]

(b) Test the hypothesis that there is no difference in the mortality rate between the factories and England and Wales. Comment on your findings.

[7 MARKS]

(c) Calculate a 95% confidence interval for the SMR. Interpret your findings.

[4 MARKS]

(d) Suggest one further analysis you might wish to undertake to examine the causality issue.

[2 MARKS]

7. A randomised controlled trial was undertaken to compare medical and surgical treatment for stable angina pectoris. 768 patients were randomised and the main outcome was death within two years. The results were as follows:

	Assigned surgical treatment			Assigned medical treatment		
	Actual medical treatment	Actual surgical treatment	Total	Actual medical treatment	Actual surgical treatment	Total
Survivors	20	354	374	296	48	344
Deaths	6	15	21	27	2	29
Total patients	26	369	395	323	50	373

Source: European Coronary Surgery Study Group (1979)

(a) Perform an intention-to-treat analysis on these data to test whether there is any difference between medical and surgical treatment. Interpret your findings.

[10 MARKS]

(b) Estimate the death rates for an explanatory analysis.

[2 MARKS]

(c) A further trial of this question is planned. How many patients would be required to have a 90% chance of finding a difference between the treatments at the 5% level? Justify any assumptions made about estimated death rates.

[Hint: For a binary outcome, the number per group required to find a difference at the 100(1 - α)% significance level with 100(1 - β)% power is given by

$$n = \frac{2}{\Delta^2}\left[\Phi^{-1}\left(\frac{\alpha}{2}\right) + \Phi^{-1}(\beta)\right]^2 \text{ where } \Delta = \frac{p_2 - p_1}{\sqrt{\bar{p}(1-\bar{p})}},\ \bar{p} = \frac{p_1 + p_2}{2}$$

where p_1 and p_2 are the estimated proportions on the two treatments respectively.]

[8 MARKS]