Statistics Assignment

Due Date 31 January 2008

Statistics Assignments must be received at the College Office 12 months prior to sitting the Part II examinations.

Two (2) copies of the Statistics Assignment are required to be forwarded to the College Office. The cover sheet should include your name, but should ONLY be noted on that sheet, as assignments are ascribed a number to ensure blind marking.

- Candidates who commenced training prior to 1 January 2002 are required to submit their statistics assignments at least six months prior to sitting the Part II examination.

  Candidates who commenced training from 1 January 2002 are required to submit their statistics assignments at least twelve months prior to sitting the Part II examinations and are also required to meet the trainee research requirement described earlier in the handbook.

You are required to answer five questions three questions relating to issues of study design, randomisation and sample size and critically apprising two published papers.

Whilst detailed theoretical statistical knowledge is not required, the appropriateness of statistical methods will be expected. Reasonable understanding of concepts such as confidence intervals, p-values, sample sizes and their respective merits are expected together with an understanding of clinical trials design. Some knowledge of the assumptions underlying the use of various statistical methods is essential.

Candidates should feel free to suggest more efficient statistical/design methods if appropriate.

The two published papers (questions 4 and 5) require a comprehensive critical appraisal. The appraisal involves an understanding and scientific comment with respect to:

a) the appropriateness of the scientific design
b) the conduct of the study
c) whether statistical methods used were the most appropriate
d) whether the analyses addressed the hypotheses originally formulated
e) the appropriateness of the conclusions

Simply summarising the article is not satisfactory and in the past candidates who simply summarised the findings of the article with little original comment will not constitute a satisfactory result – critical evaluation of the study conclusions based on (a)-(e) are being sought.

Answers to each question should be *no more* than 2000 words

QUESTION 1

Patients in intensive care units (ICU) are often given "compression' stockings to prevent deep venous thrombosis (DVT). However, there are two questions related to using these compression stockings:

i. Is thigh-length compression stocking better/worse than a knee-length stocking?
ii. Is the position in which the patient lies important? (Two standard positions are used for unconscious ICU patients - either on back with legs out straight, or on side with knees bent at about 60 degrees)

A pilot study is suggested using blood flow in the veins of the legs as a surrogate outcome for both of the two research questions. Blood flow can be measured using Doppler ultrasound. However, the investigators suspect that there is an interaction between compression stocking effectiveness and position of the patient. The hypothesis is that thigh-length stocking will be better when the legs are straight, and the knee-length one will be better when knees are bent (due to excess compression behind the knee from the thigh-length stocking). The investigators plan to perform this study on healthy volunteers (their colleagues!). There is no reason to suggest that the stockings permanently affect blood flow, and that blood flow returns to 'normal' when the stocking is removed

a. Discuss possible designs that would be appropriate to evaluate the two questions of interest.
b. Detail which outcomes you would use, and suggest when measurements be taken.
c. Outline a randomisation scheme and identify potential stratification factors.

QUESTION 2

A geriatrician wants to conduct a randomised trial to assess the value of a coordinated care team approach (similar to that used in specialist geriatric wards) in reducing length of stay and patient functioning (e.g. ability to carry out the basic activities of daily living – bathing, toileting, eating, walking) for elderly, frail patients in acute medical care wards. Patients will be assessed for frailty on emergency department (ED) admission using standard criteria (which include dementia, recent stroke, falls, depression etc.)

The allocation of the 'treatment' is dependent on the hospital ward assigned to patients when admitted through the ED. The intervention treatment consists of patient assessment by a clinical nurse specialist, recruitment of all relevant team members to care for the patient, and the prescription by them of interventions such as physiotherapy, occupational therapy, social work and medical care according to a set of evidence-based clinical guidelines. This intervention is provided in one acute medical ward only. This will be compared with 'usual care' treatment where, upon ED admission, patients are assigned to another acute medical ward with no specifically assigned nursing or health care intervention for geriatric care.

The study will be conducted in a medium-sized public hospital, with no geriatric unit. There are two acute medical wards (one which provides the intervention care, the other which provides usual care). Elderly patients present to the ED, where those who are to be admitted are allocated to one of the acute care wards on the basis of bed availability. If a bed is not available in either ward, they are allocated to either another ward or held in the ED until a bed becomes available. Most patients come under the care of general physicians who practice over both wards, and patients are allocated to them based on workload (each general physician can have a pre-specified maximum number of patients allocated to them). A minority of patients who would meet the study eligibility criteria will be admitted under other specialists (around 10%). Patients who have been admitted before under a general physician are re-admitted under the same general physician as previously. Nursing staff are generally allocated permanently to a particular ward, but may work in other wards for occasional shifts. It is estimated that there will be 5-6 study patients (i.e. approximately 3 intervention and 3 control) out of the total 32 acute care beds in the wards at any one time.

a. Suggest potential designs for running this trial and discuss the 'pros and cons' for each potential design.
b. Discuss these alternative designs in terms of 'contamination'/dilution effects of the intervention in the control group. The investigators are particularly concerned that control patients may receive the intervention (or a modification of the intervention). This is due to staff seeing the intervention being delivered and/or staff being required to sometimes work in the ward providing cares for the control patients, and thus starting to provide a similar standard of care for all patients. Suggest a trial design that would allow you to measure this contamination effect.
c. What is your suggested procedure for randomising patients to either intervention or control?
d. Will you stratify by any factors and if so, by which factor(s)?
e. Discuss any other issues that might affect the ability of the trial to answer the study question.

QUESTION 3

Faecal incontinence (FI) remains a therapeutic problem in many patients when conservative measures (i.e., medical treatment using antidiarrheals) fail and sphincter repair is unsuccessful or inappropriate. Biologic or artificial neosphincters are a therapeutic option in these cases, but these treatments have a significant failure rate and high associated morbidity. (A neosphincter is a small, fluid-filled device that is completely implanted within the body. Once placed, no parts are visible. It is designed to mimic the natural function of the anal sphincter muscle, giving you control over bowel movements.) This condition has been known to be the result induced in patients receiving radiation therapy for the treatment of prostate cancer.

Sacral nerve stimulation (SNS), which has been successfully used for urologic incontinence, is an alternative approach. This involves inserting a small device into the sacral plexus (provides nerves for the pelvis and lower limbs), which delivers regular electrical stimulation to the sacral nerve system, thus encouraging regular muscle contractions in the lower pelvic area. Its clinical results appear to be excellent with an approximate overall 80% success rate in controlling faecal incontinence in patients with a neurologically intact sacral plexus and an anatomically intact anal sphincter and rectum. Despite the clinical benefit of this technique, the mechanism of action of SNS is still unclear. However, until now, all studies except one were performed without a randomized control group, making it impossible to completely exclude a placebo effect. Modern design of permanently implanted SNS devices allows for the device to be either activated (ON) or not activated (OFF), unbeknown to the patient.

A number of gastroenterologists have approached you to help design a study investigate the efficacy of a permanently implanted SNS device compared to standard treatment (use of antidiarrheals). The patient population of interest is those with faceal incontinence severe enough to cause patients to remain at home at least once per week to avoid incontinence accidents. It is known that standard treatment in these patients is inadequate and it is hoped that SNS will provide an improvement in outcome. It is thought that patients suffering FI for more than 18 months have a different aetiology than those for who only recently acquired the condition.

It is estimated that around 35 patients per year would be prepared to participate in a trial evaluating various treatment options for faecal incontinence and it is planned that all patients will be managed through a single institution.

a) Discuss the value of a 'run-in' phase for this problem.
b) Design a study to evaluate the benefit of the SNS device. Consider two possible designs (parallel & cross-over) and provide the relative merits of each design. Which design would you recommend? Provide a schema diagram as well.
c) Given your recommendation in part (b), provide details of potential study endpoints/outcomes [primary and secondary], their measurement, study duration.
d) Provide an appropriate randomisation scheme (you will need to consider method & potential stratification factors).
e) A sample size of 50 patients has been agreed upon as being feasible target for the study. The investigators are further interested in examining immediate (within 3 months) and long term (24 months) potential benefit of the intervention. Modify the design proposed in (b) to accommodate such an evaluation (all comparisons need not necessarily be a randomised).

QUESTIONS 4 and 5: Scientific appraisal

Question 4

BMJ 2004;328;129-; originally published online 7 Jan 2004;
Stephen Bridgman and Julia Brown
R, Garry R, Fountain J, Mason S, Hawe J, Napp V, Abbott J, Clayton R, Phillips G, Whittaker M, Lilford. The eVALuate study: two parallel randomised trials, one comparing laparoscopic with with abdominal hysterectomy, the other comparing laparoscopic with vaginal hysterectomy *BMJ* 2004;328: 129-36.

Question 5

Klimo P, Thompson CJ, Kestle J, Schmidt M. A meta-analysis of surgery versus conventional radiotherapy for the treatment of metastatic spinal epidural disease. *Neuro-Oncology* 2005;7: 64–76

Suggested Resources:

S. Pocock., Clinical Trials : A Practical Approach John Wiley

S. Gore & D. Altman: Statistics in Practice British Medical Journal

Guidelines for the Pharmaceutical Industry on the Preparation of Submissions to the Pharmaceutical Benefits Advisory Committee: Commonwealth Department of Human Services & Health Nov. 1995

Altman, D Practical Statistics for Medical Research Chapman & Hall

The following references may be useful in obtaining guidance regarding critical appraisal of the literature:

Evidence based medicine what it is and what it isn't. Sackett, D et. al BMJ 312 pp71-72. 1996

Evidence Based Medicine Working Group, McMaster University Health Sciences Centre. Evidence-based medicine – A New Approach to teaching and practice of medicine. JAMA 268(17) pp 2420-2425. 1992

Users' Guides to the Medical Literature

1. How to Get Started JAMA 270(17), pp 2093-2095. 1993

2. How to Use an Article About Therapy or Prevention
    A. Are the Results of the Study Valid? JAMA 270(21), pp 2598- 2601.1993.

    B. What Were the Results and Will They Help me in Caring for My Patients? JAMA 271(1), pp 59-63.1994

3. How to Use an Article About a Diagnostic Test
    A. Are the Results of the Study Valid? JAMA 271(5), pp 389- 391.1993

    B. What Were the Results and Will They Help me in Caring for My Patients? JAMA 271(9), pp 703-707.1994

4. How to Use an Article About Harm. JAMA 271(20), pp 1615- 1619.1994

5. How to Use an Article About Prognosis JAMA 272(3), pp 234- 237.1994

6. How to Use an Overview. JAMA 272(17), pp 1367-1371.1994

7. How to Use a Clinical Decision Analysis
    A. Are the Results of the Study Valid? JAMA 273(16), pp 1292- 1295.1995

    B What Were the Results and Will They Help me in Caring for My Patients? JAMA 273(20), pp 1601-1613.1995

8. How to Use Clinical Practical Guidelines
    A. Are the Recommendations Valid? JAMA 274(7), pp 570-574.1995

    B What Were the Recommendations and Will They Help You in Caring for Your Patients? JAMA 274(20), pp 1630-1632.1995

9. How to Use an Article on Economic Analysis of Clinical Practice
    A. Are the Results of the Study Valid? JAMA 277(19), pp 1552-1557.1997

    B What Are the Results and Will They Help Me in Caring for My Patients? JAMA 277(22), pp 1802-1806.1997

10. Clinical Trials in Oncology Interdisciplinary Statistics: S. Green., J. Benedetti and J. Crowley. Chapman & Hall, 1997

11. Introducing New Treatments for Cancer: Practical Ethical and Legal Problems. (ed. C.J. Williams). 1992, John Wiley

12. J. Elwood., Casual Relationships in Medicine. A Practical System for Critical Appraisal. Oxford University Press, 1988.

13. Fletcher, R., Fletcher S., and Wagner E. Clinical Epidemology, the Essentials 2nd.edn 1988. Williams and Wilkins Baltimore.

You may wish to refer to notes kindly provided by Dr Gail Ryan on methods of critical appraisal which may be downloaded from this website

Additionally the series of articles edited by A Keech & V Gebski in the Medical Journal of Australia may provide useful background reading:

Gebski VJ, Beller EM, Keech AC. Randomised controlled trials: elements of a good study. *Medical Journal of Australia* 2001; 175: 272–274.

Ghersi D, Gebski VJ, Keech AC. Scientific background and rationale for a randomised controlled trial. *Medical Journal of Australia* 2001; 175: 386.

Keech AC, Gebski VJ. Selecting participants for clinical trials. *Medical Journal of Australia* 2001; 175: 490–491.

Brighton J, Gebski VJ, Keech AC. Specifying interventions in a clinical trial. *Medical Journal of Australia* 2002; 176(6): 281-282.

Gebski V, Marschner I, Keech AC. Specifying objectives and outcomes for clinical trials. *Medical Journal of Australia* 2002; 176(10): 491-492.

Kirby A, Gebski V, Keech AC. Determining the sample size in a clinical trial. *Medical Journal of Australia* 2002; 177(5): 256-257.

Keech AC, Gebski V. Managing the resource demands of a large sample size in clinical trials: can you succeed with fewer subjects? *Medical Journal of Australia* 2002; 177(8): 445-447.

Beller EM, Gebski V, Keech AC. Randomisation in clinical trials. *Medical Journal of Australia* 2002; 177 (10): 565-567

Forder PM, Gebski VJ, Keech AC. Allocation concealment and blinding: when ignorance is bliss. *Medical Journal of Australia* 2005; 182(2): 87–89.

Cakir B, Gebski VJ, Keech AC. Flow of participants in randomised studies. *Medical Journal of Australia* 2003; 178(7): 347–349.

Hague WE, Gebski VJ, Keech AC. Recruitment to randomised studies. *Medical Journal of Australia* 2003; 178(11): 579–581

Gebski VJ, Keech AC. Statistical methods in clinical trials. *Medical Journal of Australia* 2003: 178(4): 182-184

Burgess DC, Gebski VJ, Keech AC. Baseline data in clinical trials. *MJA* 2003; 179(2): 105-107.

Heritier SR, Gebski VJ, Keech AC. Inclusion of patients in clinical trial analysis: the intention-to-treat principle. *Medical Journal of Australia* 2003; 179 (8): 438-440

O'Connell RL, Gebski VJ, Keech AC. Making sense of trial results: outcomes and estimation. *Medical Journal of Australia* 2004; 180: 128–130

Cook DI, Gebski VJ, Keech AC. Subgroup analysis in clinical trials. *Medical Journal of Australia* 2004; 180: 289–291

Simes RJ, Gebski VJ, Keech AC. Subgroup analysis: application to individual patient decisions. *Medical Journal of Australia* 2004; 180(9): 467–469

Keech AC, Wonders SM, Cook DI, Gebski VJ. Balancing the outcomes: reporting adverse events. *Medical Journal of Australia* 2004; 181(4): 215–218.

Lord SJ, Gebski VJ, Keech AC. Multiple analyses in clinical trials: sound science or data dredging. *Medical Journal of Australia* 2004; 181(8): 452–454

Seale JP, Gebski VJ, Keech AC. Generalising the results of trials to clinical practice. *Medical Journal of Australia* 2004; 181 (10): 558–560