BIO STATISTICS COLLABORATION OF AUSTRALIA

Study Guide

Clinical Biostatistics [CLB]

Semester 1, 2021

Prepared by:
Annette Dobson, Mark Jones, Michael Coory, Peter Baker, Michael Waller and others
School of Public Health
University of Queensland

THE UNIVERSITY OF QUEENSLAND AUSTRALIA

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1. Introduction

This unit or course comprises four topics that are important for practising biostatisticians, especially those working in clinical settings or, more generally, evidence-based health care. Each topic is covered in a module designed to take 2 or 4 weeks to complete. Each module is more or less independent and comprises a study guide, readings, and exercises. There are 3 assignments, one covering modules 1 and 2, and the other two covering modules 3 and 4 respectively.

Workload requirements

The expected workload for this unit is 10-12 hours per week on average, consisting of guided readings, discussion posts, independent study and completion of assessment tasks.

Assumed knowledge

The following BCA units are recommended pre-requisites (*co-requisite).

MBB: Mathematical Background for Biostatistics
EPI: Epidemiology
PDT: Probability and Distribution Theory
DES: Design of Randomised Controlled Trials
PSI: Principles of Statistical Inference
*LMR: Linear Models

2. Contacts

The coordinator and lecturer for this course is Michael Waller whose contact details are:

School of Public Health, Public Health Building
University of Queensland
Herston Road, Herston QLD 4006
E-mail: m.waller@uq.edu.au
Office phone: 07-3365-5116;

If you have difficulties contacting the coordinator or lecturer, or would like to discuss your BCA program in general, please contact the BCA HQ.

E-mail: bca@ctc.usyd.edu.au

3. Learning Objectives

Overall Objectives

1. Understand and apply Continuous Quality Improvement to medical studies and hospital data including detection of special and common causes of variation
2. Explain and apply appropriate measures of agreement and consistency for both raters and continuous measurements
3. Calculate measures of the performance of diagnostic tests and interpret these via ROC curves where appropriate
4. Describe systematic reviews and undertake meta-analyses of various types of studies
5. Understand advantages and disadvantages of cross-over designs in general and be able to analyse 2x2 designs
6. Explain the role of, and the relationships between, non-inferiority, efficacy and equivalence trials
7. Calculate and report sample sizes for non-inferiority and equivalence trials
8. Choose the appropriate graphical and/or statistical methods to answer clinical questions
9. Effectively communicate the results of, and ideas behind statistical analyses performed to clinicians and statisticians

The *specific objectives* of each module are as follows. On completion of the modules you should be able to:

Module 1: Statistical Process Control

- Understand the concepts of Continuous Quality Improvement and their usage
- Distinguish between Special Causes and Common Causes of variation
- Detect Special Causes of variation using a Shewhart control chart
- Detect Common Causes of variation using a CUSUM control chart
- Detect Common Causes of variation using a EWMA chart

Module 2: Clinical Agreement

- Explain the concepts of validity and reliability of measurements
- Explain the concepts of agreement and consistency between 2 or more measures how, for continuous measurements, these relate to simple correlation or regression
- Use appropriate graphical and analytical methods to assess agreement between 2 raters using continuous, nominal or ordinal category measurement using Bland-Altman methods and kappa statistics

- Use appropriate intra-class correlations for agreement and consistency involving more than 2 raters using continuous scale measurements

Module 3: Diagnostic Tests, Systematic Reviews and Meta-Analysis

- Calculate measures of performance of a diagnostic test: sensitivity, specificity, and likelihood ratios.
- Translate the pre-test probability of disease for a particular patient into post-test, predictive values.
- Plot and interpret a ROC curve.
- Calculate the diagnostic odds ratio and explain its relationship to the ROC curve.
- Explain the rationale for doing systematic reviews, rather than narrative reviews.
- Describe the steps involved in undertaking a systematic review.
- Conduct a meta-analysis for various study types (including RCTs, observational studies and diagnostic tests) and various outcome variables.
- Estimate and interpret heterogeneity across studies.

Module 4: Clinical Trials

- Understand the advantages and disadvantages of using cross-over trials
- Be able to prepare appropriate graphical displays of cross-over trial data
- Be able to analyse 2x2 cross-over trials with a continuous response using both t-tests and analysis of variance
- Be able to produce point estimates and confidence intervals for the parameters of interest in a 2x2 cross-over trial with a continuous response
- Understand the underlying assumptions of these analyses and be able to perform appropriate model checks
- Be able to analyse 2x2 cross-over trials with binary outcomes
- Be able to estimate the sample size required for a 2x2 cross-over trial.
- Understand the difference between equivalence and efficacy designs
- Appreciate the impact of such designs on analysis principles, e.g. intention-to-treat, especially in the presence of non-compliance.
- Be able to work out the sample size needed in equivalence designs and understand the difference with a similar calculation in a standard efficacy trial
- Get some exposure to non-inferiority studies, their role and link with equivalence trials
- Be able to work out the sample size needed in non-inferiority studies
- Have an idea on internal validity of equivalence/non-inferiority studies

4. Method of Delivery & Communication

The unit materials are available on the BCA eLearning site, along with the data sets for exercises and assignments. Addtional materials such as copies of journal articles will be emailed to you. If you wish the unit materials will be posted to you, with a copy of this guide.

We would like to encourage the use of the discussion board facilities on the eLearning site, in order to try and reduce the isolation of studying by distance. Firstly, you will see a 'Student Introductions' forum on the discussion board. You can add your own information to this forum, if you wish, so that others in the course can contact you. For example:
Jonathan Bloggs
j.bloggs@ctc.edu.au
ph: 02-9999-9999
NHMRC Clinical Trials Centre, Sydney
Jonathan is a trainee biostatistician at the Clinical Trials Centre. He is currently working with trials of new medications for diabetes and heart disease.

This is entirely optional. If you would like to be part of the forum, but without your contact details, that will be fine as well.

When you log in to the eLearning site, you will see under 'Discussions' various forum headings. We will include some general discussion points in each module to encourage discussion amongst the group, but would like you to discuss matters and help each other as much as you can. Some students in the past have said they haven't used the discussion board as much as they would have liked, as they didn't want to be seen to be colluding in the preparation of assignments. We encourage discussion about the course material, and assignments, as long as worked answers are not given. Based on feedback from previous students we are no longer allocating any marks for participation in discussions.

Outline solutions to the exercises in each module (except those to be submitted for assessment, as described below) will be posted online at the midway point of the allocated time period for the module. This is intended to encourage you to attack the exercises independently (or via the eLearning site), and yet not make you wait too long to see the sketch solutions.

Assignments will be sent, and marks posted using the eLearning assessment tool. In 2021, submission will be via *TurnItIn* for all assignments.

Recommended approaches to study

Students should work through each module systematically, following the module notes and any readings referred to, and working through the accompanying exercises. You will learn a lot more efficiently if you tackle the exercises systematically as you work through the notes. You are encouraged to post any content-related questions to eLearning, whether they relate directly to a given exercise, or are a request for clarification or further explanation of an area in the notes. You should also work through all of the computational examples in the notes for yourself on your own computer.

Method of communication with coordinator

We encourage you to maintain regular contact with the coordinator and get in touch with them if you have any problems.

Questions about administrative aspects or course content can be emailed to the coordinator, and when doing so please use "(CLB):", "BCA", "Clinical Biostats" or similar in the Subject line of your email to assist in keeping track of our email messages. Coordinator/s will be available to answer questions related to the module notes and practical exercises, and to address any other issues that require clarification. However, please note that instructors are not necessarily available every day of the week and you should expect that it may take a day or so to respond to questions (possibly longer over weekends and during breaks!).

We strongly recommend that you post content-related questions to the Discussions tool in the CLB area of BCA's eLearning site. In 2021 we are using the Learning Management system hosted by the University of Sydney. You may be familiar with the system from previous BCA units, and will receive any specific instructions on using the eLearning site this semester from the BCA Coordinating Office. There is also a "Getting Started" document available on the Student Resources page of the BCA website.

5. Unit Materials

The course consists of four modules. Each module has some brief notes to guide your reading and study. The modules usually begin with an overview paper, generally written from a more clinical perspective, in order to orient you to the significance of the topic, and to put it in context of real-world clinical problems. The rest of the readings in each module then give more statistical depth to the topic. An exception to this format is the module on clinical trials where the notes are self-contained. We have chosen to present this course using mainly journal articles, rather than a textbook. Firstly, there is no textbook that covers all the topics. Secondly, reading journal articles and extracting the relevant information to the problem at hand is part of the real-world experience of a practising biostatistician. It is not an easy skill to develop! We suggest you practise summarising what you did learn, and what you could not decipher from each article. Then go to the discussion board and see if you can work it out with your fellow students. You should also work through all of the computational examples in the notes for yourself on your own computer. Materials are changed from year to year in response to student feedback and the availability of new, better materials.

For each topic we will upload a short video to go with the material for that topic. The videos are mostly power-point presentations with slides and an audio track that will hopefully enhance the written material. Other formats will be trialled. Each module includes exercises which you should work through, and for which outline solutions will be posted on the eLearning site for CLB as each module progresses.

6. Software

For this course you will need access to software that can perform the various analyses required for the exercises and assignments. *R or Stata* is recommended, although students have successfully completed

this course using *SAS*. *Excel* is also quite useful for several modules. Data sets for the course are provided on the CLB eLearning site.

7. Textbooks

There is no recommended textbook for this course. Readings are provided for each module instead.

8. References

The main readings from journal papers and textbooks are provided with each module. Additional resource materials are provided on the CLB eLearning site.

9. Assessment

The assessment is based entirely on the assignments. There is no examination. Details of assignments are given in the modules. These assignments will be posted on the eLearning site together with an online Announcement broadcasting their availability. They are in the form of written reports. They must follow a logical form, employ correct English and contain relevant, well labelled tables and figures (noting that raw computer output is not acceptable). We suggest you consider writing your assignments in a similar fashion to a journal article, with clearly defined aims, methods, results and conclusions. The following two documents available on the BCA website as resources for current students may be helpful:

Guidelines for Reporting Statistical Results
Referencing Style Guide

The dates for submitting the assignments are listed below (see Timetable). For the first 2 modules there is an assignment worth 30% (15% for each module). There is an assignment worth 35% for each of modules 3 and 4 (see the table below). All assessment must be submitted to pass the course.

Assessment	Coverage	Type	Learning Objectives	Weight
Assignment 1	Modules 1 & 2	Report	1,2,8,9	30%
Assignment 2	Module 3	Report	3,4,8,9	35%
Assignment 3	Module 4	Report	5,6,7,8,9	35%

In general, you are required to submit your work typed in Word or similar although converting to PDF may prove useful prior to submitting via Turnitin,

Before commencing the course, you should read the BCA assessment guide (Appendix), and the information about the plagiarism policy of your home university.

Assessment deadlines are important.

Extensions or late submissions policy

The standard BCA policy for late penalties for submitted work is a 5% deduction from the earned mark for each day the assessment is late, up to a maximum of 10 days (including weekends and public holidays). Extensions are possible, but these need to be applied for (by email) as early as possible. The Unit Coordinator is not able to approve extensions beyond three days; for extensions beyond three days you need to apply to your home university, using their standard procedures.

Extensions can cause delays in feedback for other students who submitted on time. Also due to prerequisites, late results may preclude you from studying subsequent units. Different universities have different result submission deadlines. BCA results have to be transmitted between universities, which shortens the available time.

10. Timetable

Each module is scheduled to begin on a Monday and conclude on the Sunday of the specified week.

Week	Dates	Module	Co-ordinator	Due date for Assignment
1	March 1 - 7	1	Michael Waller	
2	March 8 – 14	1		
3	March 15 – 21	2		
4	March 22 – 28	2		Assignment 1 set March 22
5	March 29 – April 4	3		
6	April 5 – 11		Mid semester break & public holidays	Assignment 1 due April 5 for Modules 1-2
	April 12 – 18	3		
7	April 19 – 25	3		
8	April 26 – May 2	3		Assignment 2 set April 26
9	May 3 – 9	4		
10	May 10 – 16	4		Assignment 2 due May 10 for Module 3
11	May 17 – 23	4		
12	May 24 – 30	4		Assignment 3 set May 24
				Assignment 3 due June 7 for Module 4

11. Complaints policy

Please see the BCA complaints policy in the Assessment Guide and in online assessment submission pages.

12. Summary of recent changes to materials and/or procedures

In 2012 there was an external review of the BCA curriculum which recommended several changes including no longer offering a unit on Advanced Clinical Trials. The most important parts of that unit were to be moved to DES and CLB, with DES and PSI becoming pre-requisites for CLB. The full implementation of these recommendations has taken time, with universities' approvals needed and then the changes to DES had to be made before the changes to CLB could be introduced.

This is the third offering of the revised version of CLB. To accommodate the new Module 4 on Clinical Trials we have reduced and re-arranged the other modules. This has been achieved by removing concepts and methods that are less commonly used in biostatistical practice and eliminating many of the readings. Additionally, in response to student feedback, we have reduced the number of assignments from 4 to 3.

Feedback is always welcomed to improve the units. As part of the BCA commitment to continuous quality improvement your feedback about this revised unit is especially important.