# BIO
## STATISTICS
### COLLABORATION
### OF AUSTRALIA

**Study Guide**

Clinical Biostatistics (CLB)

Semester 1, 2025

Prepared by:
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**Contents**

## Clinical Biostatistics (CLB)
**Semester 1, 2025**

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Dr. Nasir Moghaddar is the coordinator and lecturer for this course.

If you have any general BCA queries, please contact the BCA Coordinating Office on 02 9562 5076/54 or email bca@sydney.edu.au

## Background

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.

## Context within the program

This course is an elective unit.

Prerequisites
The following BCA units are recommended pre-requisites:
MFB: Mathematical Foundations for Biostatistics
EPI: Epidemiology
PSI: Principles of Statistical Inference

Co-requisites
The following BCA units are suggested co-requisites that may be taken before or concurrently:
RM1: Regression Modelling for Biostatistics 1

## Unit summary

This unit covers a range of statistical methods including statistical process control (special and common causes of variation; quality control charts), clinical agreement (Bland-Altman methods, kappa statistics, intraclass correlation), diagnostic tests (sensitivity, specificity, ROC curves), systematic reviews and meta-analysis (systematic reviews, assessing heterogeneity, publication bias, estimating effects from randomised controlled trials, diagnostic tests and observational studies), and Clinical Trials (equivalence trials, cross-over trials).

## Workload requirements

The expected workload for this unit is 8-12 hours per week on average, consisting of guided readings, discussion posts, independent study and completion of assessment tasks.

## Learning Outcomes

At the completion of this unit students should be able to:

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 2×2 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

## Unit content

The unit is divided into 4 modules, summarised in more detail below. Each module will involve approximately 2 to 4 weeks of study and includes the following material:

1. Module notes describing concepts and methods, and including some exercises of a more "theoretical" nature.

2. Selected readings from published articles or textbooks.

3. One or more extended examples illustrating the concepts/methods introduced in the notes and including more practically oriented exercises.

Study materials for all Modules are accessed from the eLearning unit site. Assignments and supplementary material such as datasets will be available within each Assignment item. Please note that we are not able to post copies of copyright material (journal articles and book extracts)—for these you will have to rely on your home university's library.

## 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 should also work through all the computational examples in the notes for yourself on your own computer.

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 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.

Make the most of this unit by engaging with coordinators and fellow students on the Discussion Board and in Tutorials. These are safe spaces to discuss the course material and related ideas and students are encouraged to make the most of them by engaging in respectful discussion. Videos of the live tutorials will also be posted on the eLearning site after each tutorial.

Questions about Assignments should be directed to the coordinator in the first instance to avoid any Academic Honestly issues.

## Method of communication with coordinator(s)

We strongly recommend that you post content-related questions to the Discussion Board in the CLB area of BCA's eLearning site. In 2023 we are using the Canvas 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 in Canvas" document available on the Student Resources page of the BCA website.

Questions about administrative aspects or course content can be emailed to the coordinator. Please use "(CLB):" 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. 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!).

At the start of semester, we will send a welcome email. The course notes are available on the BCA eLearning site, along with the data sets for exercises and assignments. However, some readings may not be available on the BCA eLearning site hence these may be emailed to you.

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.

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. We encourage discussion about the course material, as long as assignment answers are not given.

## Module descriptions

Below is an outline of the study modules, followed by a timetable and assessment description table.

Each module is scheduled to begin on a Monday and conclude on the Sunday of the following week.  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 2×2 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 2×2 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 2×2 cross-over trials with binary outcomes
- Be able to estimate the sample size required for a 2×2 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

## Unit schedule

Below is an outline of the study modules, followed by a timetable and assessment description table.

Semester 1, 2025 starts on Monday 03 March 2025

| Week | Week commencing | Module | Assessment |
|------|-----------------|--------|------------|
| 1 | 03 March 2025 | 1 | |
| 2 | 10 March 2025 | 1 | |
| 3 | 17 March 2025 | 2 | Assignment 1 available Friday 21 March 2025 |
| 4 | 24 March 2025 | 2 | |
| 5 | 31 March 2025 | 3 | **Assignment 1 due Friday 04 April 2025** |
| 6 | 07 April 2025 | 3 | |
| 7 | 14 April 2025 | 3 | |
| | 21 April 2025 | Mid-semester break | |
| 8 | 28 April 2023 | 3 | Assignment 2 available Monday 28 April 2025 |
| 9 | 5 May 2023 | 4 | |
| 10 | 12 May 2023 | 4 | **Assignment 2 due Monday 12 May 2025** |
| 11 | 19 May 2023 | 4 | Assignment 3 available Friday 16 May 2025 |
| 12 | 26 May 2023 | 4 | |
| 13 | 02 June 2023 | | **Assignment 3 due Friday 30 May 2025** |
| | | | |

## Assessment

Assessment will include 3 written assignments. For the first 2 modules there is an assignment worth 30%. There is an assignment worth 35% for each of modules 3 and 4 (see the table below).  Each assessment is to be completed within approximately 2.5 weeks. **Assessments are due by 05:00 pm (QLD time) on the stated day.**

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:

Guide for Reporting Statistical Results
Referencing Style Guide

| Assessment name | Assessment type | Coverage | Learning objectives | Weight |
|---|---|---|---|---|
| Assignment 1 | Assignment | Modules 1-2 | 1, 2, 8, 9 | 30% |
| Assignment 2 | Assignment | Module 2 | 3, 4, 8, 9 | 35% |
| Assignment 3 | Assignment | Module 3 | 5, 6, 7, 8, 9 | 35% |

In general, you are required to submit work typed in Word or similar, although converting to PDF may prove useful prior to submitting via Turnitin. We strongly recommend you become familiar with equation typesetting software such as Microsoft's Equation Editor for algebraic work. See the BCA Assessment Guide for guidelines on acceptable standards for assessable work.

Students are encouraged to discuss relevant topics in the Discussion Board. However, please avoid posting questions relating directly to assessable material.  These should be emailed to the Unit Coordinator in the first instance.

*Explicit solutions to assessable exercises should not be posted for others to use.* Each student's submitted work must be clearly their own, with anything derived from other students' discussion contributions clearly attributed to the source.


**Submission and academic honesty policy**
All assessment material should be submitted via the relevant Assessment module in Canvas unless otherwise advised. Turnitin plagiarism detection is applied to all submissions. For detailed information, please see the BCA Assessment Guide, which includes links to the Academic Honesty policies at member universities.  Please familiarise yourself with the procedures and policies at your home university.  You will need to indicate your compliance with the plagiarism guidelines and policy at your home university.

*A special note regarding "contract cheating" sites:* Unfortunately, there have been instances in the past of students using such websites to post assignment questions and receive solutions (usually for a fee).  We have arrangements with these sites to identify the student posting questions or accessing the solutions, and such students will be referred to and face disciplinary processes at their home university.

Use of ChatGPT or other generative AI tools
The assessment tasks in this Unit have been designed to be challenging, authentic and complex.  Although individual assessment components may provide specific guidance regarding the use of generative artificial intelligence (AI) tools (e.g., ChatGPT),

successful completion of these components will require students to critically engage in specific contexts and tasks for which AI will provide only limited support and guidance. In all cases, a failure to reference the use of generative AI may constitute student misconduct under the Student Code of Conduct of your University of enrolment. To successfully complete assessment tasks, students will be required to demonstrate detailed comprehension of their written submission independent of AI tools.

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**Late submission and extension procedure**
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 can approve extensions up to three days; for extensions beyond three days, you must apply to your home university, using their standard procedures.

## Learning resources

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 in both *R* and *Stata* will be posted on the eLearning site for CLB as each module progresses.

## Software requirements and assumed knowledge

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.

Stata 13 was released in June 2013, and we assume you are using at least this version. However, we expect most of you would be using Stata 14-17, the latter of which was released in April 2021. We are not aware of any major differences between Stata versions that affect the material, but minor issues will be pointed out in Blackboard postings. If you only have an earlier version of Stata (v12 or earlier) then please email me (Louise) and we can discuss your options. Importantly, whichever version you are using, please ensure that you have performed the online update to the latest update of that version. (Use the command update query.)

For SAS, some modules provide SAS scripts for examples, however these are provided for completeness and are not assessable.

For help with R, please see [Learning R](#) in the Student Resources site. For help with Stata please use the help functions within Stata.

If you have not yet organised access to these packages, you should do so as soon as possible. This is a practical course which requires regular use of the relevant software; delays in gaining access to these packages may impact your ability to complete the course. Information on how to download R and RStudio, and access Stata can be found in the *BCA Textbook and Software Guide*.

## Required mathematical background

Students who have undertaken the pre-requisites will have the required mathematical background for the course. This unit is practical in nature and is focused on the application of a range of statistical methods on datasets using statistical software.

## Feedback

Our feedback to you:

The types of feedback you can expect to receive in this unit are:

- Formal individual feedback on submitted exercises assignments
- Feedback from non-assessed online quizzes during tutorials
- Responses to questions posted on Discussion board

Your feedback to us:

One of the formal ways students provide feedback on teaching and their learning experience is through the BCA student evaluation survey at the end of each semester. The feedback is anonymous and provides the BCA with evidence of aspects that students are satisfied with and areas for improvement.

## Unit changes, including response to recent student evaluation

Clinical Biostatistics (CLB) was last delivered in Semester 2 2023. 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.

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; have increased the number of tutorials from 4 to 6; and have included more recent STATA commands for meta-analysis.

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.

## Acknowledgements

We acknowledge Prof Annette Dobson, A/Prof Mark Jones, Prof Michael Coory, Dr Peter Baker and Dr Michael Waller who have developed earlier versions of the CLB units and other materials which have been included as part of this delivery.