BIO STATISTICS COLLABORATION OF AUSTRALIA

# Study Guide

# Design of Randomised Controlled Trials (DES)

# Semester 2, 2024

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THE UNIVERSITY of ADELAIDE

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**Design of Randomised Controlled Trials (DES)**
**Semester 2, 2024**

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

## Welcome letter

Welcome to Design of Randomised Controlled Trials (DES). Experimental designs play a critical role in the conduct of medical research. Underpinning evidence-based medicine are well-conducted randomised controlled trials, which form a basis for clinical practice. A solid introduction to principles of experimental design and issues related to randomised controlled trials is important to facilitate experiments having optimum statistical efficiency.

This unit is delivered through the eLearning site at the University of Sydney. All course content other than readings will be uploaded to eLearning, including assignments and supplementary material. Discussions of material will take place on the Discussion Board. There is currently an Introductions thread on Discussion Board; please use this thread to introduce yourself to the rest of the class. This unit requires access to one of two statistical software packages: R and / or Stata (detailed shortly) for Module-3. You should organise access to at least one of these as soon as possible.

If you have any questions or issues, please contact me by email. My email address is lynne.giles@adelaide.edu.au or you can contact me via the Canvas page links. I hope you enjoy the course!

Lynne Giles
July 2024

## Background

This subject will introduce randomised comparisons as a major tool used in medical research and the basis of providing evidence for improving clinical practice. This is a one semester course and will be offered in distance learning mode only.

## Context within the program

This course differs somewhat from many of the other BCA units in the program in that it does not require much in the way of 'hands on' analysis or application of formulae (though there is some of this)! It mainly involves working through principles and concepts and applying these to real life situations and problems likely to be encountered in the design of trials. Most of the examples and assessment questions are based on actual studies. In many situations there is not necessarily a correct or incorrect answer. What is of importance is the appropriate discussion and consideration of relevant issues.

In keeping with the above philosophy, the course material is based around published articles and extracts from books. The use of eLearning is very important in this course as it provides a guide to the course material and opportunities for discussion and clarification of concepts. You are strongly encouraged to make the most of the Discussion Forums to ask questions about course-related administration, clarify concepts and to understand the relevance of the articles provided.

The **prerequisite** courses are:
Epidemiology (EPI)
Mathematical Background for Biostatistics (MBB) or Mathematical Foundations for Biostatistics (MFB)

## Unit summary

This unit is designed to enable students to understand and apply the principles of design and analysis of experiments, with a particular focus on randomised controlled trials (RCTs). A variety of topics will be covered, including different randomisation schemes, commonly used study designs, and Phase I-IV experimental studies. There will be consideration of sample size and analytical approaches including intention-to-treat analyses, interim analyses and the handling of missing data. On successful completion of this unit, students will be able to effectively as a statistician to the planning, conduct and reporting of a standard RCT.

## 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.

## Learning outcomes

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

1. Identify the benefits of randomisation as a mechanism for reducing bias, and implement a variety of randomisation schemes.
2. Demonstrate knowledge of the principles behind the common experimental designs.
3. Describe the efficiency advantages of crossover designs, and be able to design and interpret the two-period crossover study.
4. Demonstrate an understanding of the principles underlying Phase I, II, III and IV studies, as well as an appreciation of the scientific basis underlying issues in clinical

studies including intention-to-treat, blinding, interim analyses, subgroup analyses and the handling of missing data.

5. Appreciate the importance of sample size in clinical studies, and perform sample size calculations for a variety of trial designs with different outcomes.

## Unit content

The unit is divided into 5 modules, summarised in more detail below. Each module will involve 2 or 3 weeks of study and generally includes the following material:

1. Module notes describing concepts and methods, and including some exercises that have conceptual and application orientation.
2. Selected readings from published articles or textbooks.
3. One or more extended examples illustrating the concepts/methods introduced in the notes and more practically oriented exercises.

Study materials for all Modules are downloadable from the eLearning unit site. Assignments and supplementary material, such as datasets, will be posted to the unit site. 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 resources from 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 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.

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.

## Method of communication with coordinator

Lynne Giles is the unit coordinator and instructor for Semester 2 2024. Her email is lynne.giles@adelaide.edu.au

Questions about administrative aspects or course content can be emailed to the coordinator, and when doing so please use "DES:" 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 DES area of BCA's eLearning site. The BCA uses the University of Sydney

online Learning Management (eLearning) System (LMS), called **Canvas**. For information on eLearning, see the BCA Introduction to eLearning. Once you have read the instructions and the login advice provided by BCA office staff you may login at: canvas.sydney.edu.au

Module notes, data files and other documents will be made available on eLearning. Assignments and course announcements will likewise be uploaded to eLearning. Communication should generally be via the Discussion Board on eLearning (unless of a personal/confidential nature). You are encouraged to post questions, ideas, suggestions and discussions on eLearning. The Course Coordinator will monitor and respond to communication; however, you are encouraged to answer other students' questions or assist in solving problems (with the exception of assignment question queries, which I will clarify).

## Module descriptions

Below is an outline of the study modules, followed by a timetable and assessment description table.
*Please note: All assignments are to be submitted by 11:59pm on the due date shown in the course timetable.*

**Module 1: Introduction to Randomised Controlled Trials**

Overview:

This module provides the rationale for experimental studies in medical research and outlines the main principles of experimental studies, in particular randomised controlled trials (RCTs). Various methods of randomisation of patients to treatments within RCTs are discussed.

Aims:

This module aims to:

1. Provide students with an introduction to the main concepts of experimental studies and RCTs, including the rationale for RCTs, and an overview of the features of randomised studies.
2. Provide students with an understanding of the various methods of randomisation used in RCTs, and the advantages and disadvantages of commonly used randomisation schemes.

**Module 2: Design of RCTs**

Overview:

This module outlines some of the study designs used in randomised controlled trials (RCTs), including parallel designs, crossover designs and n-of-1 trials, and introduces the issue of missing data in RCTs

Aims:

This module aims to provide students with an understanding of the features, advantages and disadvantages of the common study designs for RCTs.

**Module 3**: **Sample Size**

Overview:

This module covers concepts important to understanding and calculating sample size for various types of outcomes and study designs.

Aims:

This module aims to provide an understanding of issues important for sample size, such as types of errors, significance level and power, and provide students with practical experience in calculating sample size for different outcomes and study designs.

**Module 4**: **Phase I and Phase II Studies- Interim Analysis and Early Stopping**

Overview:

This module covers design and analysis issues for Phase I and Phase II clinical trials and provides an overview of the issues of interim analyses and early stopping in clinical trials.

Aims:

This module aims to:

1. Provide students with an understanding of the purpose, design, and analysis/ interpretation of Phase I (dose finding) and Phase II (safety and efficacy) clinical trials.
2. Provide students with an understanding of when interim analyses are appropriate, and design and analysis issues relating to interim analyses and criteria for early stopping in clinical trials.

**Module 5: Analysis and Reporting of RCTs**

Overview:

This module introduces issues associated with the analysis and reporting of RCTs and outlines the problems of multiplicity (i.e. multiple outcomes or multiple analyses) and of missing outcome data in RCTs.

Aims:

This module aims to provide students with:

1. An understanding of issues surrounding the analysis and reporting of RCTs.
2. A basic understanding of the issues associated with multiple outcomes and multiple analyses in RCTs.
3. A basic understanding of the issues associated with missing outcome data in RCTs.

## Course timetable

Semester 2, 2024 starts on Monday 29th July.

| Week | Week Commencing | Module | Topic | Assessment |
|---|---|---|---|---|
| 1 | 29 July 2024 | Module 1 | Introduction to RCTs | |
| 2 | 5 August 2024 | Module 1 | Introduction to RCTs | |
| 3 | 12 August 2024 | Module 2 | Design of RCTs | Assignment #1 – Available 16 August |
| 4 | 19 August 2024 | Module 2 | Design of RCTs | |
| 5 | 26 August 2024 | Module 3 | Sample Size | |
| 6 | 2 September 2024 | Module 3 | Sample Size | ***Assignment #1 - Due 2 September (30%)*** |
| 7 | 9 September 2024 | Module 4 | Phase I and Phase II Studies | Assignment #2 – Available 13 September |
| 8 | 16 September 2024 | Module 4 | Phase I and Phase II Studies | |
| | ***23 September 2024*** | | ***Mid Semester Break – 1 week only*** | |
| 9 | 30 September 2024 | Module 4 | Phase I and Phase II Studies | ***Assignment #2 - Due 30 September (30%)*** |
| 10 | 7 October 2024 | Module 5 | Analysis and Reporting of RCTs | |
| 11 | 14 October 2024 | Module 5 | Analysis and Reporting of RCTs | Assignment #3 – Available 18 October |
| 12 | 21 October 2024 | Module 5 | Analysis and Reporting of RCTs | |
| 13 | 28 October 2024 | | Revision | |
| | 4 November 2024 | | | ***Assignment #3 – Due 4 November (40%)*** |

## Assessment

The assessment for this unit will involve three written assignments which will be posted on eLearning 2.5 weeks prior to the submission date. Assessments are due by 11:59pm on the due date.

| Assessment name | Assessment type | Coverage | Learning objectives | Weight |
|---|---|---|---|---|
| Assignment 1 | Assignment | Modules 1 & 2 | 1, 2 | 30% |
| Assignment 2 | Assignment | Modules 3 & part 4 | 3, 4, 5 | 30% |
| Assignment 3 | Assignment | Modules 1-5 | 1-5 | 40% |

Module solutions/guides will be posted on eLearning after the submission date. Individual feedback on assignments will be provided to each student.

Students are expected to monitor eLearning for the posting of assignments, solutions and feedback. Email notifications and other channels of communication will not be used.

Examples and exercises are contained in each module to enable students to ascertain their level of understanding of various topics. These will not form part of the assessment of this course.

In general, you are required to submit your work typed in Word or similar (e.g. using Microsoft's Equation Editor for algebraic work) and we strongly recommend that you become familiar with equation typesetting software such as this. If extensive algebraic work is involved you may submit neatly handwritten work, however please note that marks will potentially be lost if the solution cannot be understood by the markers due to unclear or illegible writing. This handwritten work should be scanned and collated into a single pdf file and submitted via the Canvas site. See the BCA Assessment Guide document for specific 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 in assessment tasks**
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 AI tools (e.g., ChatGPT), successful completion of these components will require students to critically engage in specific contexts and tasks for which artificial intelligence 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.

**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 text book for this subject is:

> Friedman, L.M. Furberg, C.D., DeMets, D.L., Reboussin, D.M., Granger, C.B. (2015) Fundamentals of Clinical Trials. 5th edition. Cham: Springer International Publishing.

It will be necessary for you to have access to this book, as some of the course material is contained in the text book. You may be able to access a copy through your place of employment or a local library. It is also available for purchase at online sites. It is freely available online at many of the universities in the BCA consortium.

## Software requirements and assumed knowledge
For this subject you will need to have access to either Stata Version 14 and above, or R, or any online sample size calculator packages. If using online software then please note that certain commands in module 3 will not work as these are written for Stata software only.

## Required mathematical background
Students who have undertaken the pre-requisites will have the required mathematical background for the course.

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

- Formal individual feedback on submitted exercises and assignments
- Feedback from non-assessed online quizzes
- Responses to questions posted on Canvas

Your feedback to us:

One of the formal ways students provide feedback on teaching and their learning experience is through the BCA student evaluations at the end of each unit. 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

DES was last delivered in Semester 2 2023. Major changes were made to DES in 2007 and 2008 and more recently in 2015 following a BCA curriculum review. A unit review was conducted in Semester 1 2024, and some of the changes suggested in that review are being incorporated in the Semester 2 2024 delivery. Additional changes have been made in response to student feedback. Sections in the notes that generated a large amount of discussion have been updated, as have the reading materials and software programs made available. In 2018 there was a change in Module 3, related to sample size estimation, with the section on non-compliance revised following discussion with senior triallists. Following recent student feedback, the changes that have been made to the unit delivery are: electronic copies of module notes without the reading list will be left on Canvas until 15th November; detailed feedback on the evaluated assignments will be provided within two weeks of their submission; and updates to the course material to reflect the text book by Friedman et al. Stata software references for Module 3 were updated in 2022 and 2024. At the request of students, more videos and additional online sessions at a range of times were added to the unit in 2022 and 2023, with modifications for the delivery in 2024.

## Acknowledgments

Design of Randomised Controlled Trials was originally designed and written by Cate D'Este at The University of Newcastle, and by Val Gebski and Rachel O'Connell at The University of Sydney. Substantial modifications were made in 2007 and 2008 by Philip Ryan, Amy Salter, Gary Glonek, Lisa Yelland and Tom Sullivan at The University of Adelaide. Further modifications were made in 2015 by Amy Salter, Jennie Louise and Tom Sullivan at The University of Adelaide, in 2018 by Murthy Mittinty at The University of Adelaide, and in 2024 by Lynne Giles.