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## Study Guide

# Design of Randomised Controlled Trials (DES)

Semester 2, 2021

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Prepared by:  
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## **Design of Randomised Controlled Trials (DES)**

**Semester 2, 2021**

### **Instructor contact details**

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### **Other Contacts**

If you have trouble contacting the academic coordinator/academic staff, or have any other queries, please contact:

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BCA Coordinating Office  
Biostatistics Collaboration of Australia BCA  
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Email: [bca@ctc.usyd.edu.au](mailto:bca@ctc.usyd.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 two statistical software packages: R and Stata (detailed shortly) for Module-3. You should organise access to these as soon as possible.

If you have any questions or issues, please contact me by email at the address above. I hope you enjoy the course!

Murthy Mittinty  
July 2021

## **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.

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.

## Course content

The unit is divided into 5 modules, summarised in more detail below. Each module will involve approximately 2 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 contained in your mail-out package and are additionally 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.

## 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.

## 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

Murthy N Mittinty is the course coordinator and instructor.

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**. The LMS has been transferred from Blackboard to Canvas in 2-2018. 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](https://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).

## **Text Book**

The text book for this subject is:

Matthews, J.N.S. Introduction to Randomized Controlled Clinical Trials, (Second Edition) Chapman & Hall/CRC Texts in Statistical Science

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.

## **Software**

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.

## **Prerequisites**

Epidemiology (EPI)  
Mathematical Background for Biostatistics (MBB)

## **Co-requisites**

None

## Learning Outcomes

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

Identify the benefits of randomisation as a mechanism for reducing bias, and implement a variety of randomisation schemes.

1. Demonstrate knowledge of the principles behind the common experimental designs.
2. Describe the efficiency advantages of crossover designs, and be able to design and interpret the two-period crossover study.
3. 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.
4. Appreciate the importance of sample size in clinical studies, and perform sample size calculations for a variety of trial designs with different outcomes.

## Module descriptions

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

**The due date for submission of Assignment is 11:59pm on the day is due to be submitted.**

### Module 1: Randomisation

#### 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



Aim:

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, 2021 starts on Monday 26<sup>th</sup> July.

| Week | Week Commencing   | Module   | Topic   | Assessment                                |
|------|---|----------|---|---|
| 1    | 26 July 2021  | Module 1 | Randomisation   |   |
| 2    | 2 August 2021   | Module 1 | Randomisation   | Assignment # 1 – Available 9 August       |
| 3    | 9 August 2021   | Module 2 | Design of RCTs  |   |
| 4    | 16 August 2021  | Module 2 | Design of RCTs  |   |
| 5    | 23 August 2021  | Module 3 | Sample Size   | <b>Assignment #1 - Due 31 August</b>      |
| 6    | 30 August 2021  | Module 3 | Sample Size   |   |
|      | 3 September   | Module 3 | Sample size Workshop                                  | 12.00-1.00 pm not recorded. Adelaide time |
| 7    | 6 September 2021  | Module 4 | Phase I and Phase II Studies                          | Assignment # 2 Available 5 September      |
| 8    | 13 September 2021   | Module 4 | Phase I and Phase II Studies                          |   |
| 9    | 20 September 2021<br>Note: Monday is a public holiday in some states. | Module 4 | Phase I and Phase II Studies                          | <b>Assignment #2 - Due 26 September</b>   |
|      | 27 September 2021   |          | <b>Mid Semester Break 1 week only</b>                 |   |
| 10   | 4 October 2021  | Module 5 | Analysis and Reporting of RCTs / Multiple Comparisons | Assignment # 3 – Available 4 October      |
| 11   | 11 October 2021   | Module 5 | Analysis and Reporting of RCTs                        |   |
| 12   | 18 October 2021   | Module 5 | Analysis and Reporting of RCTs                        |   |
| 13   | 25 October 2021   |          | Revision  |   |
|      | 1 November 2021   |          |   | <b>Assignment #3 – Due 1 November</b>     |

## Assessment

The assessment for this unit will involve three written assignments.

- Assignment 1 will cover Modules 1 and 2 and will be worth 30%.
- Assignment 2 will cover Modules 3 and 4 and will be worth 30%.
- Assignment 3 will cover Module 5, as well as Modules 1-4, and will be worth 40%.

Assignments will be posted on eLearning three weeks prior to the submission date. 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 eLearning site. See the [BCA Assessment Guide](#) document for specific guidelines on acceptable standards for assessable work.

The instructor will generally avoid answering questions relating directly to the assessable material until after it has been submitted, but we encourage students to discuss the relevant parts of the notes among themselves, via eLearning. However **explicit solutions to assessable exercises should not be posted for others to use**, and each student's submitted work must be clearly their own, with anything derived from other students' discussion contributions clearly attributed to the source.

## Submission of assessments and academic honesty policy

Please refer to the [BCA Assessment Guide](#). The guide has detailed instructions for presenting, submitting and downloading assignments.

The BCA pays great attention to academic honesty procedures. Please be sure to familiarise yourself with these procedures and policies at your university of enrolment. Links to these are available in the BCA Student Assessment Guide.

## Extensions

For various reasons, you may sometimes experience difficulties in getting your assignments submitted on the due date. Requests for an extension for an assignment must be made **in advance of the due date for that assignment**. The normal grounds

for an extension being granted are bereavement, personal illness or illness in a family member requiring you to exercise a significant carer role.

These requests must be made directly to Murthy Mittinty by email. Murthy will note the date and time of the request and reply to the request by email with the decision as to whether an extension has been granted and, if so, stating the length of the extension.

*Length of extension:* Extensions granted by Unit Coordinator will normally be no longer than two days.

## **Penalties for late submission**

BCA policy states: Unless otherwise stated, a student can submit an assessment up to 10 days after the due date. A late penalty of 5% per day will be applied (including weekends and public holidays). The maximum penalty which can be applied is a reduction to 50%.

Submissions after the solutions have been posted on eLearning will not be awarded any marks.

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.

## **Assignment Cover Sheet**

Where assignment work is submitted online using the Assignment tool in canvas you will be able to indicate your compliance with the plagiarism guidelines and policy by electronic means. In this case, you do not need to complete the DES 2021 Assignment Cover Sheet.

If you submit work by another method, then you do need to complete the DES 2021 Assignment Cover Sheet, in which you will be asked to certify that the submission is your own work and that you have read the policy of the university at which you are enrolled. The cover sheet can also be downloaded from canvas. If you are posting your submission, please include the signed cover sheet in the envelope.

If you are submitting via email, please scan the signed cover sheet and submit this with your assignment, or fax the signed cover sheet to the number specified on the sheet.

Please refer to the [BCA Assessment Guide](#) for further information.

## **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
- Responses to questions posted on Blackboard

Your feedback to us:

One of the formal ways students have to 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.

### **Changes to DES since last delivery, including changes in response to student evaluation**

DES was last delivered in Semester 2 2020. Major changes were made to DES in 2007 and 2008 and more recently in 2015 following a BCA curriculum review. 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 has been a change in Module-3, sample size estimation, with the section on non-compliance revised following discussion with senior trialists. Following recent student feedback the changes that have been to the course delivery are; the soft copies of module notes without the reading list will be left on canvas till 5<sup>th</sup> of November, provide detailed feedback on the evaluated assignments within two weeks of their submission, and to implement further updates on the course material to reflect the text book by Matthews. Stata software references for Module-3 have been updated since last delivery in 2018. At the request of students this year, 2021, I will add more videos and have made the date of workshop as part of the time table.

### **Acknowledgments**

This course, 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 and again in 2018 by Murthy Mittinty.