

## Syllabus for HCEP 512

This is a survey course looking at key issues in the design and analysis of clinical trials.

### Week 1 Organization

In week 1, we examine organizational issues which are key in the success of clinical trials. Many trials today involve multiple centres, and thus the many management decisions which must be taken into consideration before during and after the trial are as important to the success of a trial as its design. As well, resource needs must be carefully assessed and distribution of resources must be planned. We will also examine the design of case report forms and the importance of consultation with personnel that will be handling the data at various phases of the study.

### Week 2 Design Issues

We consider the relative merits of the randomized controlled trial (RCT) and other types of designs, and then consider a variety of options with the RCT design including choice of the control group, factorial and cluster designs and non-inferiority trials, and review some of the CONSORT suggestions for the design and reporting of a trial. We will focus on the concept of confounding and how the different designs deal with confounding.

### Week 3 The study population

Defining the eligibility criteria for a trial has huge implications for external validity (to what conditions can the trial be generalized?) and sometimes to the internal validity (is the comparison between treatment groups fair and unbiased?). We examine the considerations which weigh on the decision to design a trial as pragmatic (as similar as possible to existing clinical conditions, and thus highly generalizable) and explanatory (tightly controlled and hence a proof of the concept that the treatment can have value at least in carefully designed circumstances). Issues in planning recruitment to a trial will also be discussed.

### Week 4 The mechanics of RCTs

We will examine the concepts of randomization, stratification, and blinding and their implications for controlling bias. Since not all interventions are subject to blinding we will examine how design features can be used to help deal with lack of blinding. We will also consider whether blinding ought always to be used when it

can be. We will also consider the importance and relevance of the presentation of baseline characteristics, the situations in which baseline characteristics are most likely to have impact on study interpretation, and techniques that can be used to adjust for baseline differences.

#### Week 5 Sample Size Calculations

Historically, one of the biggest problems of RCTs has been that they have been undersized to detect important clinical differences. In this section, we will consider some of the basic issues in determining sample sizes and examine common errors. We will discuss the necessary characteristics for presentation of sample size in the context of a research proposal, including the consideration of loss to follow-up, and the use of the literature to justify the estimates used in sample size calculation.

#### Week 6 Outcomes

The discussion focuses on the definition of outcomes, issues related to the decision about the primary outcome, and the validity of composite (combined) outcomes and surrogate outcomes. We also focus on “analytic strategy”; how do we decide which patients should be included in the analysis, the issue of missing data, and the potential for bias in analysis. We will consider the metrics of defining treatment effects.

#### Week 7 Health Status/Quality of Life Measurement

Particularly for chronic conditions where treatments may or may not delay progression of disease, health status/quality of life measurement is an important patient reported outcome that should help to define optimal outcome. Because the measurement issues pertaining to defining these sorts of outcomes are different and complex, we devote a week to discussing this, focusing on the concepts of validity, reliability and responsiveness, barriers to the use and interpretation of quality of life instruments, and the difference between disease-specific and generic instruments.

#### Week 8 Multiplicity

Multiplicity (or multiple analyses) enters trials in many different ways. We will examine the way that multiplicity enters trials with specific examples from the literature and look at ways that investigators can deal with multiplicity so that “positive” results do not reflect excessive false positive errors. Included in the discussion will be examples of repeated looks over times (sequential analysis),

repeated measures over time, multiple outcomes, multiple (>2) treatment groups, subgroup analysis and multiple analytic strategies. Much focus is given to subgroup analysis and the concept of statistical interaction.

#### Week 9 Sequential Analysis and the Data Safety Monitoring Board

We examine the problem of sequential analysis (examining RCT data as it is accumulated over time), evaluate alternative solutions that have been offered to resolve this problem, and explore the role of the DSMB in evaluating trials over time, both with regard to interim analyses and other factors which may affect the outcome and interpretation of the study.

#### Week 10 Crossover Trials

One way to control the variability when we randomize participants to alternative treatments is to have all participants receive both treatments but in random order. We examine the advantages and limitations of the randomized crossover trial. We also examine the use of baseline characteristics as a method to reduce variability in comparing groups and compare different ways of defining outcome when using baseline characteristics (change scores versus percentage change versus adjusting for baseline with regression).

#### Week 11 Regression Models

This week we look at the use of regression models in the evaluation of outcomes in RCTs, including continuous outcomes (linear regression), binary outcomes (logistic regression), and time-to-event outcomes (survival/Cox regression). What should they be used for, and what shouldn't they be used for. We will examine the use of survival models in particular, and their interpretation.

#### Week 12 Meta-analysis, Ethics

The first part of the class will consider the use of meta-analysis and systematic review to combine the results of clinical trials. How do these formal methods advance science and what are their limitations?

The second part of the class will focus on some of the key ethical issues in RCTs, including informed consent and clinical equipoise.