Dalla Lana School of Public Health, University of Toronto

CHL 5225 H – Advanced Statistical Methods for Clinical Trials

Website: www.andywillan.com/CHL5225H/index.htm

Instructors

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1) Overview:

Academic and professional statisticians are frequently included as co-investigators on clinical trials. Their responsibilities as a co-investigator usually include trials design, involving issues of randomization, stratification and sample size determination, as well as statistical data analysis, reporting and presentation. Consequently, there is substantial demand from academia and the pharmaceutical industry for graduate level statisticians with training and experience in advanced statistical methodology for clinical trial. In response to that demand this course has been designed to provide exposure to the advanced statistical methods used in clinical trials for students seeking graduate degrees in biostatistics or statistics. The intended student population is meant to be graduate students in biostatistics and statistics.

2) Teaching objectives:

a) To gain an understanding of language and methodology of clinical trials.
b) To gain proficiency in advanced statistical methods in the design of clinical trials.
c) To gain proficiency in advanced statistical methods in the analysis of clinical trials.

3) Course prerequisites:

Bachelor's degree in biostatistics or statistics or the equivalent, and a thorough understanding of mathematical statistics, calculus and matrix algebra.

4) Format of instruction:

There will be 3 hours of lectures each week. There will be four homework data sets. Each data set will include methodological and computational exercises.

4.1 Role of data sets: The only way to learn new statistical methods is to perform them on real or realistic data sets. Therefore, analyzing homework data sets is crucial to mastering these methods. The data sets will attempt to expose students to the typical issues that arise when analyzing clinical trials data.

4.2 Computing: Computing is a vital part of this course. Students will need to be familiar with either R, Splus or SAS, if not at the beginning, then by the end of the course. These programs are available on PC clusters on the fifth floor of Health Sciences Building (155 College Street) and on the first floor of the Medical Science building. Alternatively, one year license maybe purchased from the university's site license centre.

5) Timetable of Curriculum Topics:

Week 1. The Language of Clinical Trials (AW)

- Phases of clinical trials
- Randomization, concealment, blocking stratification
- Blinding, placebos and sham treatments
- Effectiveness versus efficacy
- Intent-to-treat principle
- Designs: parallel, crossover, cluster, multi-centre, multi-national, large simple, factorial
- Patient follow-up
- Approaches to analyses
- Typical report of results

Week 2. Crossover Trials (AW)

- Appropriate health conditions
- Appropriate treatments
- Period and carryover effects
- Using the maximum statistics
- Higher order designs

Week 3. Introduction to Survival Analysis in Clinical Trials (KT)

- Nonparametric
    - Failure times & censoring times; hazard functions, survivor functions
    - Kaplan Meier curves, standard error
- Log rank tests and other alternatives
- Relationship between f(t), S(t), h(t)
- Parametric models
    - Exponential, Weibull
    - Concepts of proportional hazards and accelerated failure time

Week 4. Models for Survival Data Analysis with Covariates (JR)

- Proportional hazards model
    - Exponential model for covariates
    - Partial likelihood
    - Testing proportional hazards
    - Estimating relevant functional forms for covariates
    - Time dependent covariates
    - Recurrent events and multiple endpoints

Week 5. Cluster Randomized Trials (KT)

Weeks 6 & 7. Longitudinal Data Analysis in Clinical Trials (JR)

- Summary measures of longitudinal data
- Techniques for plotting longitudinal data
- Generalized Estimating Equation (GEE) models
- Random effects models
- Dropouts

Week 8. Multiplicity (KT)

- Multiple outcomes – toxicity versus efficacy
- Multiple analyses
- Futility analysis

Week 9. Sample Size Determinations (JR)

- Continuous outcomes
- Dichotomous outcomes
- Time to event outcomes
- Longitudinal outcomes
- Cross-over trials
- Pilot studies, equivalence trials

Week 10. Sample Size for Time to Event Analysis (MP)

- Introduction to competing risks
- Sample size for competing risks
- Sample size for case cohort study
- Using simulation for power calculation.

Week 11. Bayesian Approaches for Clinical Trials (AW)

- Bayesian definition of probability
- Making simple, intuitive and meaningful statement of inference

Weeks12. Cost-effectiveness Analysis (AW)

- Incremental cost-effectiveness ratios
- Incremental net benefit
- Covariate adjustment

Week 13. Value of Information Methods (AW)

- Bayesian Decision Theory
- Optimal Trial Design