Dalla Lana School of Public Health, University of Toronto

CHL 5225 H – Advanced Statistical Methods for Clinical Trials

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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 three homework data sets. Each data set will include methodological and computational exercises. Each student will also work on an individual project for classroom presentation. The presentation project can be the presentation of (i) a recent statistical methodology paper pertaining to clinical trials, (ii) an interesting statistical methodology issue in a recently published report of a clinical trial or (iii) the presentation of the analysis of data from a real (non-trivial) clinical trial. The topic for each project must be approved by the a course instructor. A written report of the presentation project is also required

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.

4.3 Presentation Project: Students will be required to do a project for presentation. The presentation project can be the presentation of (i) a recent statistical methodology paper pertaining to clinical trials, (ii) an interesting statistical methodology issue in a recently published report of a clinical trial or (iii) the presentation of the analysis of data from a real (non-trivial) clinical trial. The topic for each project must be approved by the course instructors.

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

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

- Relationship between f(t), S(t), h(t)
- Parametric models
    - Exponential, Weibull
    - Concepts of proportional hazards and accelerated failure time
- Proportional hazards model
    - Exponential model for covariates
    - Partial likelihood
    - Estimation of baseline hazard

Week 5. Extensions to Cox Model (MP)

- Proportional hazards model continued
    - Testing proportional hazards
    - Estimating relevant functional forms for covariates
    - Interval censoring
    - Time-dependent covariates
    - Strata and time-dependent strata
- Competing risks, recurrent events and multiple endpoints
- Informative censoring

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

- Summary measures of longitudinal data (absolute change, rate of change, percentage change, area under the curve)
- GEE models, Random effects models
- Dropouts
- Quality-of-life data

Weeks 8. Cost-effectiveness Analysis (AW)

- Incremental cost-effectiveness ratios
- Incremental net benefit
- Covariate adjustment
- Expected value of information

Week 9. Sample Size Determinations (JR)

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

Week 10. Value of Information Methods (AW)

- Bayesian Decision Theory
- Optimal Trial Design

Week 11. Multiplicity (KT)

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

Week 12. Cluster Randomized Trials (KT)

Week 13. Meta Analysis ()

6) References:

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