Introduction to Statistical Methods for Clinical Trials

Olli Saarela

Dalla Lana School of Public Health
University of Toronto

olli.saarela@utoronto.ca

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Clinical and epidemiological research
Clinical research

- A definition (Miettinen 2011, p. 139):
  
  *research intended to serve advancement of the (scientific) knowledge-base of clinical medicine – of the knowledge base of gnosis in clinical medicine*

- Miettinen 2011, p. 15:
  
  *Gnosis – In medicine, a doctor’s esoteric knowing about the health of a/the client*

- The three subtypes of medical gnosis are:
  1. Diagnosis
  2. Prognosis
  3. Etiognosis
Clinical medicine and community medicine

➤ Miettinen 2011, p. 18:

*Medicine – A professional’s pursuit and attainment of esoteric knowing about the health of the client – medical gnosis, that is – and teaching the client (or a representative of the client) accordingly.*

*Clinical medicine – That segment of medicine in which individuals are cared for, one at a time.*

*Community medicine (synonym: epidemiology) – That segment of medicine in which ‘communities’ – populations (jurisdictional, occupational, . . .) – are cared for as populations, rather than as individuals one at a time.*
Trials

- Analogously, epidemiological research is aimed at advancing the knowledge-base of community medicine.
- Epidemiological research is largely *observational* (more precisely: *non-experimental*), whereas clinical research is more commonly *experimental*.
- Miettinen 2011, p. 158:

  *Randomized controlled trial (synonyms: randomized trial, clinical trial) – An experimental intervention-study, one in which the allocations to the contrasted interventions are based on randomization.*
Control

► Miettinen 2011, p. 159:

*The meaning of ‘control’ in this context is not that there is experimental control of the allocations to the contrasted interventions; this is the meaning of ‘trial’ (i.e., ‘experiment’). Instead, the meaning is this: In studying the effect(s) of a particular intervention, experience with a cohort subjected to this intervention shows only what happens with this intervention; the experience does not show what would have happened without this intervention. To learn about the latter, a ‘control’ cohort subjected to the intervention’s alternative is included in the trial.*

► If a trial is randomized, it is necessarily also controlled.
Experimental and non-experimental research
Motivating example

- Comparative effectiveness of partial and radical nephrectomy in the treatment of renal cell carcinoma.
- The partial procedure is aimed at removing the tumor, while preserving as much of the kidney function as possible.
- However, not removing the whole kidney might leave some cancer cells intact, possibly increasing the risk of local recurrence of the disease.
- How to study the comparative effectiveness in a non-experimental setting?
A non-experimental study

- In clinical practice kidney cancer patients are assigned to the radical or partial procedure based on various indications.
- After surgery, the patients are monitored for progression (recurrence or metastasis) of the disease.
- The times from surgery to disease progression can be compared between the two procedures in routinely collected clinical data.
- We are interested in the relationship

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procedure type -> progression-free survival
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Kaplan-Meier curves

Progression-free survival

Partial nephrectomy
Radical nephrectomy

Years since nephrectomy
Cox regression

Call:
coxph(formula = Surv(time.to.prog, progression) ~ factor(extent),
       data = ds)

   n= 1603, number of events= 174

    coef  exp(coef)   se(coef)      z     Pr(>|z|)    
factor(extent)Radical 1.0317 2.8059 0.1683 6.132 8.68e-10 ***

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Signif. codes:  0 ’***’ 0.001 ’**’ 0.01 ’*’ 0.05 ’.’ 0.1 ’ ’ 1

    exp(coef) exp(-coef) lower .95 upper .95
factor(extent)Radical  2.806 0.3564   2.018     3.902

Concordance= 0.624  (se = 0.022 )
Rsquare= 0.026   (max possible= 0.747 )
Likelihood ratio test= 41.84  on 1 df,  p=9.898e-11
Wald test            = 37.6  on 1 df,  p=8.682e-10
Score (logrank) test = 40.96 on 1 df,  p=1.555e-10
Confounding by indication

- Unfortunately, such comparisons are subject to *confounding*. (Why?)
- In particular, we are talking about *confounding by indication*.
- Patients with a more advanced disease are more likely to receive the radical procedure, but also have poorer prognosis.
- The previous results describe this, but give little evidence about the comparative effectiveness of the two procedures.
Disease progression as a confounder

▶ A corrected version of the causal graph:

Controlling for such confounding in a non-experimental study would require information on the disease progression before the surgery (what kind of information in particular?), and appropriate statistical methods.
‘The triangle’

- In a non-experimental study the arrow $X \rightarrow Z$ is present:
A randomized controlled trial removes the arrow $X \rightarrow Z$:
References