Week 7 - Intent to Treat and Non-Compliance EXAMPLES

Stat 209

Coronary Drug Project

- Randomized, multi-center, double-blind, placebo-controlled trial of clofibrate for treatment for coronary heart disease
  - 1103 men on clofibrate
  - 2789 men on placebo
- ITT analysis of 5-year mortality on clofibrate was 20.0%, 20.9% on placebo (p=0.55)

no drug effect

But, in **placebo** subjects, mortality rates at 5 years were

- Compliant: 15.1%
- Non-compliant: 28.2%

- Subjects compliant with placebo had significantly lower mortality ($p < 0.0001$)!
- The explanatory analysis would miss this effect of compliance ?

- In **clofibrate** subjects, mortality rates at 5 years were
  - Compliant: 15.0%
  - Non-compliant: 24.6%
- Subjects compliant with clofibrate had significantly lower mortality (p=0.0001)!
- Explanatory analysis – compare compliant clofibrate subjects to subjects without adequate clofibrate intake (clofibrate noncompliers and placebo subjects) – **significant**!

maybe drug good?

Actual Practice of ITT

Survey of randomized controlled trials published in 1997 in BMJ, Lancet, JAMA, and NEJM (Hollis & Campbell)

Out of 249 trials, 119 (48%) explicitly stated that an ITT analysis was performed

- 15 (13%) clearly did not analyze as randomized
- 65 (55%) appeared to analyze as randomized, but without enough detail for the readers to verify
- No consistent method for handling withdrawal

(2) Compliance -- The IV approach

Stat 209

Greenland IJE 2000

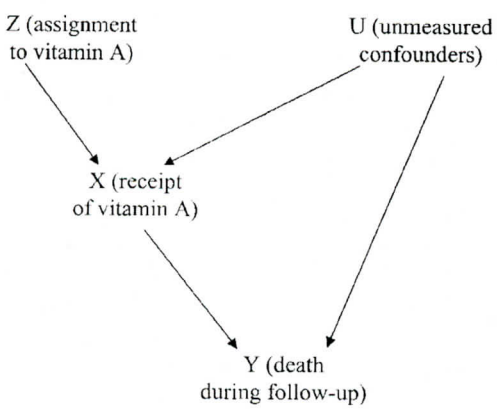

Figure 1

these concepts, Table 1 presents individual one-year mortality data from a cluster-randomized trial of vitamin A supplementation in childhood.[18,20] Of 450 villages, 229 were assigned to a treatment in which village children received two oral doses of vitamin A; children in the 221 control villages were assigned none. This protocol resulted in 12 094 children assigned to the treatment (Z = 1) and 11 588 assigned to the control (Z = 0). Only children assigned to treatment received the treatment; that is, no one had Z = 0 and X = 1. Unfortunately, 2419 (20%) of those assigned to the treatment did not receive the treatment (had Z = 1 and X = 0), resulting in only 9675 receiving treatment (X = 1). Nonetheless, assumption 1 is satisfied if the randomization was not subverted, while assumption 2 is supported by the data: Assignment to vitamin A increased the percentage receiving A from 0 to 80%.

Table 1 One-year mortality data from cluster-randomized trial of vitamin A supplementation in children.[20] Z = 1 if assigned A, 0 if not; X = 1 if received A, 0 if not

analysis in HW

	Z = 1			Z = 0	
	X = 1	X = 0	Total	X = 1	X = 0
Deaths (Y = 1)	12	34	46	0	74
Total	9675	2419	12 094	0	11 588
Risk[a]	124	1406	380	undefined	639

[a] Deaths per 100 000 within one year.

p. 2 compliance not dichotomous

Compliance Efron-Feldman (JASA 1991)

$z(u)$ compliance patient u (cholestyramine gm)

$Y_0(u)$ response y (cholest reduction) patient u if Placebo

$Y_x(u)$ response y patient u if given dose X active drug

$$Y_x(u) = G_x + (1+H_x)\,Y_0(u) + e_x(u) \qquad G_0 = H_0 = 0$$

$$\delta(x) = \bar{E}(Y_x(u) - Y_0(u)) = G_x + H_x(\bar{E}Y_0(u)) \quad \text{dose-response diff}$$

Data: ave compliance .601 $\bar{Y}_T = 32.81$, $\bar{Y}_C = 8.29$ (24.52)

note $24.52/.601 = 40.8$

difference of dose-response curve at $\delta(z)$ at z-level

$\hat{\delta}(.6) = 20.8$ $\hat{\delta}(1) = 34.5$

Compliance as an Explanatory Variable in Clinical Trials

B. Efron and D. Feldman