Issues concerning covariate adjustment in randomised trials

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Regulatory guidelines about covariate adjustment

ICH E9 Statistical Principles for Clinical Trials

- “In some instances an adjustment for the influence of covariates ... is an integral part of the planned analysis and hence should be set out in the protocol. Pre-trial deliberations should identify those covariates and factors ... and how to account for these. ... Special attention should be paid to the role of baseline measurements of the primary variable.”

CPMP Nov 2003. Points to consider on adjustment for baseline covariates. [Guidance on ICH E9]

- “Baseline imbalance itself should not be considered an appropriate reason to include a baseline measure as a covariate.”
- “When the analysis is based on a continuous outcome there is commonly the choice whether to use the raw outcome or the change from baseline. Whichever is chosen, the baseline value should be included as a covariate in the primary analysis”
- “The functional form that relates the covariates to the outcome should be pre-specified and justified.”
Outline

Parallel group trials, baseline and one followup

- Preamble: Randomised trials - unadjusted analyses
- Baseline imbalance - ramifications, adjustment (ANCOVA)
- Covariate measurement error
- Covariate is baseline of outcome
- ANCOVA comments
- Non-normal outcomes + non-linear models
Preamble: Defining a “treatment effect”

- $Y_{i1}^*$ = response of person i if that person were to receive treatment 1 (active)
- $Y_{i0}^*$ = response of person i if that person were to receive treatment 0 (control)

→ Treatment effect for person i is $Y_{i1}^* - Y_{i0}^*$

- Randomise $T_i = 1$ (active), $T_i = 0$ (control)

- Observe outcome $Y_i$ as *one* of $Y_{i1}^*$, $Y_{i0}^*$ according to trt assignment $T_i = 1$ or 0
Preamble: Population model

- Interested in broader population
  - Trial participants “random sample”
  - Aim to estimate average treatment effect
    \( \Delta \) in population (average of \( Y_{i1} - Y_{i0} \))
- Randomisation - can show
  \[ \Delta = E[Y_{i1} - Y_{i0}] = E[Y_{i1}] - E[Y_{i0}] = E[Y_i|T_i=1] - E[Y_i|T_i=0] \]
  - Can unbiasedly estimate \( \Delta \) using difference in observed means \( \bar{Y}_1 - \bar{Y}_0 \)
  - Can postulate probability models for \( Y \) given \( T \) to estimate population treatment effects
Baseline imbalance

- Randomisation guarantees baseline balance on average
- Expectation of simple difference in means is unbiased (over all randomisations/trials)
- BUT Suppose BP trial. Diff of 10mmHg b/w treatments at end of trial, but also diff of 5mmHg at baseline.
- Ignore baseline information?? OK in the long run?
Quote: Senn (1997)

“If I am cruising at 10,000m above sea level in mid-Atlantic and the captain informs me that three engines are on fire, I can hardly console myself with the thought that on average air travel is quite safe.”
Baseline imbalance

- How does observed diff in means perform when there is baseline imbalance in covariate X?

Model:  \[ Y = \alpha + \Delta T + \beta X + \varepsilon \quad (\varepsilon \sim \text{normal}) \]

\[ E[Y|T,X] = \alpha + \Delta T + \beta X \]

- Let \( D_Y = \) diff in means of outcome \( Y \)
  Let \( D_X = \) diff in means of baseline covariate \( X \)

- Then \( E[D_Y | D_X] = \Delta + \beta D_X \)
  (Conditional) “chance” bias if \( X \) prognostic and unbalanced

- Note: \( E[D_Y] = \Delta \) “unconditionally”
Does baseline imbalance matter?

- Imbalance is always due to chance (in rand trials)
  - so statistical significance tests are illogical and irrelevant
    [since Rothman 1977 ?]
  
  however

- Given observed imbalance $D_X$:
  - Type I error (size) of $D_Y$ given $D_X$ not controlled
    (Senn 1989, Pocock et al 2002)

  - Coverage of nominal 95% CI’s not correct
    - Conservative if $\rho$ large and standardised imbalance small
      ($Z_X = D_X/SE(D_X)$)
    - poor if $\rho$ and $Z_X$ large (eg 65% if $Z_X=2$ and $\rho=0.9$)
    - Large n, small baseline imbalance can be important!
Analysis of Covariance

- Bias of $D_Y$ given $D_X$ is $\beta D_X$, so $\text{ANCOVA} = D_Y - \beta D_X$
- ANCOVA answers: What would the difference b/w treatments be if the groups were balanced for covariate $X$?
ANCOVA vs unadjusted $D_Y$

- ANCOVA unbiased (cond and uncond)
  \[ \text{Var(ANCOVA)} = \text{Var}(D_Y)(1-\rho^2) \]
  - $\rho=.3$, variance is 9% lower than $D_Y$
  - $\rho=.7$, variance is 49% lower than $D_Y$

- Adjust for highly prognostic covariates whether or not imbalanced
  - Ideal if model assumptions valid.

- No point in adjusting for non-prognostic covariates even if severely imbalanced (no bias)
2. Covariate measurement error

- Unbiasedness of ANCOVA with covariate measurement error ??
- Observe $W = X + \text{error}$  [error uncorr w/X]
- Reliability $R = \frac{\text{Var}(X)}{\text{Var}(W)}$
Meas error in linear regression

- \( Y = \alpha + X\beta + \varepsilon, \ W = X + \text{error} \)
- error spreads out X’s, flattens slope (R\(\beta\))
ANCOVA Meas error model

- If “True model”: $Y=\alpha + T\Delta + X\beta + \epsilon$
  $W=X+\text{error, } X \text{ and meas error normal}$
- Then have $Y=\alpha^* + T\Delta + W R\beta + \epsilon^*$ [same $\Delta$]
- ANCOVA estimate of $\Delta$ unbiased (given $W$)!
  - Result immediate from $(Y,X,W)$ mult. Normal
  - Non-normal $X$, meas error approx true by CLT
- NOTE: Pay price in variance $= \text{Var}(D_Y)(1 - R\rho^2)$
ANCOVA with measurement error
Baseline of Outcome variable

- Consider simplest case of $Y_{\text{true}} = X + \alpha + \Delta T$
  - $Y_{\text{obs}} = Y_{\text{true}} + \text{error}, \ W = X + \text{error}$
- Define estimator: $\text{CHANGE} = D_Y - D_W$
- But - Regression to mean - diff at end of trial ($D_Y$) is expected to be less than diff at start of trial ($D_W$) due to meas error (in absence of trt effect)
  - so CHANGE overcorrects for baseline imbalance
  - Bias $= (R-1)D_w$ ($<0$ if $D_w > 0$)
- Note: CHANGE unconditionally unbiased
  - Variance $= 2\text{Var}(D_Y)(1-R)$ [uncond]
- If R low then don’t use!!
  - Can also show CI coverage problems given $D_W$ if R low
Variance of ANCOVA, POST ($D_Y$), CHANGE

![Graph showing variance of ANCOVA, POST ($D_Y$), and change for different levels of pre/post correlation.](image)
ANCOVA comments

1. Y vs X non-linear
   > potential to “shop” for p-values by fitting many forms of h(X)

2. Omitted covariates
3. Trt x covariate interaction
4. Modelling assumptions
5. Less intuitive than unadjusted analyses

1. Conditional bias, but only from non-linear component. Unbiased unconditionally
   use flexible modelling? (prespecified)
   eg fractional polynomials, smoothers

2. Unbiased unconditionally
3. If present - exists whether or not adjust!
4. Valid - Check assumptions
   - esp influential points, equal variance
5. But more efficient
   and CHANGE+X = ANCOVA
ANCOVA conclusions (linear models)

- ANCOVA is conditionally unbiased and offers efficiency gains over both $D_Y$ and CHANGE (subject to model assumptions)
- Randomisation affords robustness to meas error and model misspecification
- Prespecify covariates (eg ICH, CPMP guidelines)?
  - possible if lots of experience with condition (eg AMI, Steyerberg 2000)
  - Blinded analysis to choose model (Edwards 1999)
  - Otherwise somewhat exploratory and SE’s suspect? (Schluter+Forsythe 1985)
  - Baseline of outcome
Binary and survival outcomes

- Some surprising differences from normal theory linear models - more complex!
  - Eg Cox and logistic regression models

- Additive measurement error causes bias in treatment effect estimates

- Adjusting for perfectly balanced prognostic factors
  - *increases* standard error of trt effect estimate
  - estimate moves *away* from null
  - is estimating a *different* population parameter

Binary and survival outcomes (2)

- Continuum of popn averaged models as prognostic covariates are added
- Parameter interpretation progressively more “individualised”
- Issue of which parameter to estimate?
  - Treatment effect for individual patient?
    → adjust for all prognostic covariates?
    (eg Hauck et al 1998, Steyerberg 2000)
- Comment: GLM’s identity or log link: PA = SS useful?
References

- Rothman 1977 Epidemiologic Methods in Clinical Trials. Cancer, 39, 1771-75
- Steyerberg 2000, Clinical trials in acute myocardial infarction: Should we adjust for baseline characteristics? Amer Heart Journal, 139, 745-751