Modeling Baseline in Repeated Measures Studies

Recommendation

1. In repeated measures data, adjust for baseline as covariate in model - DO NOT include as first outcome
2. Do not use change from baseline as a response variable

Reasoning

- Baseline cannot be a response to treatment, therefore baseline and response cannot be modeled in an integrated framework (Senn, Harrell)
- Baseline tends to be best predictor of outcome post-randomization and keeping baseline on RHS will increase precision of estimated treatment effect
- Any prognostic factors correlated with outcome will also be correlated with baseline. (Harrell)
    - This reduces the need to enter a large number of prognostic variables into model
- Also, many studies have inclusion/exclusion criteria that include cutoffs on baseline and therefore baseline comes from a truncated distribution and shouldn't be modeled with same distributional shape as other timepoints. (Harrell)
- Unbiased estimator for treatment effect in many scenarios even when there are differences at baseline (Senn)
    - If factors are balanced, reduces variance of estimated treatment effect
        - Increases power
- Allows for non-linear baseline effect as opposed to Change Score which assumes no relationship between baseline and change from baseline
- If poor correlation between baseline and outcome, then Change Score will do more harm in terms of increased variability of outcome than just ignoring baseline completely as opposed to if baseline were on RHS there will not be added variability (since coefficient will be small) and will therefore be much more efficient
    - If correlation between baseline and outcome is 1, then Change Score and ANCOVA will be equally efficient; See figure in slide deck (below)
- See slides for more details
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- Even if change from baseline is response, still must include baseline as a predictor in model to avoid bias from "regression to the mean". Additionally, this can only be done in linear models (i.e. continuous outcome). Rather, one should model the raw values (Harrell)

Discussion

February 19, 2021:

1) One potential drawback to modeling baseline as predictor (ANCOVA) as opposed to as an outcome (i.e. Change Score) is the inability to set up a contrast comparing change from baseline within a treatment arm. However it is noted that Frank Harrel (see BBR (14.4) and https://discourse.datamethods.org/t/rms-discussions/3275/118 (comments 113-118)) does not recommend such a contrast when one has the ability to compare treatment arms directly since: 1) "Regression to the mean" will bias the results 2) Measurement error will bias the results. We do not yet fully understand the legitimacy of these claims and will be the topic of future discussion.

a) See References #9-10 below

2) We discussed several advantages in using ANCOVA (see attached slides for more detail). To list a few: 1) Ability to model a relationship between baseline and change (via splines) as opposed to assuming no relationship between change from baseline and baseline. 2) It is more robust than change score when dealing with imbalance at baseline (see reference #2 and Statistical Issues in Drug Discovery (Chapter 7)) 3) Less variability in outcome, especially when low correlation between baseline and outcome

References

Number	Reference	Notes

1	Regression Modeling Strategies (7.2)	
2	BBR notes (14.4)	BBR notes are freely available: https://hbiostat.org/bbr/ Video of Frank Harrell discussing this topic from his BBR notes
3	Statistical Issues in Drug Discovery (Chapter 7)	
4	https://discourse.datamethods.org/t/rms-discussions/3275/118 (see discussion from comments 113-118)	Discussion forum where I asked Frank Harrell about this topic
5	Michael G. Kenward, Ian R. White, and James R. Carpener. "Should Baseline Be a Covariate or Dependent Variable in Analyses of Change from Baseline in Clinical Trials? (Letter to the Editor)". In: Stat Med 29 (2010), pp. 1455- 1456	This is a strong rebuke of the Liu paper (see #7 below), supporting the inclusion of baseline as predictor in the model
6	Stephen Senn. "Change from Baseline and Analysis of Covariance Revisited". In: Stat Med 25 (2006), pp. 4334- 4344	Shows that claims that in a 2-arm study it is not true that ANCOVA requires the population means at baseline to be identical Refutes some claims of Liang and Zeger (see #8 below) problems with counterfactuals temporal additivity ("amounts to supposing that despite the fact that groups are different at baseline they would show the same evolution over time") Causal additivity is difficult to design trials for which simple analysis of change scores is unbiased, ANCOVA is biased, and a causal interpretation can be given temporally and logically, a "baseline cannot be a "response to treatment", so baseline and response cannot be modeled in an integrated framework as Laird and Ware's model has been used" One should focus clearly on `outcomes' as being the only values that can be influenced by treatment and examine critically any schemes that assume that these are linked in some rigid and deterministic view to `baseline' values. An alternative tradition sees a baseline as being merely one of a number of measurements capable of improving predictions of outcomes and models it in this way." "You cannot establish necessary conditions for an estimator to be valid by nominating a model and seeing what the model implies unless the model is universally agreed to be impeccable. On the contrary it is appropriate to start with the estimator and see what assumptions are implied by valid conclusions." - this is in distinction to Liang and Zeger (see #8 below)
7	Guanghan F. Liu et al. "Should Baseline Be a Covariate or Dependent Variable in Analyses of Change from Baseline in Clinical Trials?" In: Stat Med 28 (2009), pp. 2509-2530	This is a paper suggesting to use baseline as an outcome (and not predictor)
8	Kung-Yee Liang and Scott L. Zeger. "Longitudinal Data Analysis of Continuous and Discrete Responses for Pre-Post Designs". In: Sankhya 62 (2000), pp. 134-148	This is the first paper (in this discussion) which is in support of using baseline as outcome (and not predictor) Makes an error in assuming the baseline variable will have the same univariate distribution as the response except for a shift; baseline may have for example a truncated distribution based on a trial's inclusion criteria If correlation between baseline and response is zero, ANCOVA will be twice as efficient as simple analysis of change scores If correlation is one they may be equally efficient
9	J. Martin Bland and Douglas G. Altman. "Comparisons against Baseline within Randomized Groups Are Often Used and Can Be Highly Misleading". In: Trials 12.1 (Dec. 2011), p. 264. doi: 10.1186/1745- 6215- 12- 264. url: https://doi.org/10.1186/1745-6215-12-264	Describes how misleading "change from baseline" is for clinical trials
10	https://rpsychologist.com/treatment-response-subgroup	Blog discouraging using change from baseline as a statistic to identify responders
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