SISCER 2022 Module 1: Improving Precision in Estimating Marginal Treatment Effects in Randomized Trials

Michael Rosenblum, Professor of Biostatistics
Johns Hopkins Bloomberg School of Public Health
https://mrosenblumbiostat.wordpress.com

Some material from:
Benkeser, Diaz, Luedtke, Segal, Scharfstein, Rosenblum (2020) Improving Precision and Power in Randomized Trials for COVID-19 Treatments Using Covariate Adjustment, for Binary, Ordinal, or Time to Event Outcomes. Biometrics. https://doi.org/10.1111/biom.13377

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Overview

Covariate adjustment in randomized trials for estimating marginal (average) treatment effects:

- Preplanned adjustment for baseline variables when estimating average treatment effect in primary efficacy analysis.
- Target of inference (estimand) is same as when using unadjusted estimator.
- Can improve precision and reduce required sample size to achieve desired power.
- Goal: avoid making any model assumptions beyond what's assumed for unadjusted estimator (robustness to model misspecification).

Use of Covariate Adjustment in Randomized Trials: Two Surveys

Pocock et al. (2002) surveyed 50 randomized clinical trial reports.
Findings: "The statistical emphasis on covariate adjustment is quite complex and often poorly understood, and there remains confusion as to what is an appropriate statistical strategy."

Austin et al. (2010) surveyed 114 randomized trial articles.
Findings: only 39 presented an adjusted analysis.
Paper title: "A substantial and confusing variation exists in handling of baseline covariates in randomized controlled trials: a review of trials published in leading medical journals."

FDA Guidance Documents on Covariate Adjustment

1. ICH E9 Statistical Principles for Clinical Trials (1998): "Pretrial deliberations should identify those covariates and factors expected to have an important influence on the primary variable(s), and should consider how to account for these in the analysis to improve precision..."
2. FDA (2020) "To improve the precision of treatment effect estimation and inference, sponsors should consider adjusting for prespecified prognostic baseline covariates (e.g., age, baseline severity, comorbidities) in the primary efficacy analysis and should propose methods of covariate adjustment." (FDA Guidance on COVID-19 treatment and prevention trials)
3. FDA draft guidance (2021): Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products "after suitably addressing the treatment effect definition, covariate adjustment using linear or nonlinear models can be used to increase precision."

Goal of Covariate Adjustment for Marginal Treatment Effects

- Target of Inference (Estimand) is Population Average Treatment Effect, i.e., a contrast between (marginal) outcome distributions if all were assigned to treatment versus all assigned to control. (Intention To Treat)
- **Goal: Estimation of Average Treatment Effect in a Randomized Trial**.
- **If baseline variables prognostic for outcome, Covariate adjustment has potential to substantially improve precision (shorter CI's), reduce sample size, and reduce trial duration compared to unadjusted estimator.**
- Require consistent, interpretable, model-robust estimators.
- Intuition: Gain precision by adjusting for chance imbalances in prognostic baseline variables between study arms.

Some related work on covariate adjustment

Yang and Tsiatis, 2001, Zhang et al. 2008; Tsiatis et al. 2008, Rubin and van der Laan, 2008, Moore and van der Laan, 2009, Zhang and Gilbert 2010, Moore et al. 2011, Tian et al. 2012, Zheng et al. 2015, Vermuelen et al. 2015, Wager et al. 2016, Wu and Gagnon-Bartsch 2018, Zhang and Ma, 2019, Jiang et al. 2019, Wang et al. 2019, Benkeser et al. 2020.

Estimands (Targets of Inference)

Estimands (contrasts between marginal distributions under treatment and control):

- For continous outcomes: difference in means.
- For binary outcomes: risk difference, relative risk, odds ratio.
- For ordinal outcomes: difference in means, the Mann-Whitney estimand=P(random individual assigned to treatment has better outcome than random individual assigned to control), average of cumulative log odds ratios over outcome levels.
- For time-to-event outcomes: difference in survival probabilities, ratio of survival probabilities, difference in restricted mean survival times.

Estimators:

- For each estimand, these exist corresponding covariate adjusted estimators that leverage information in baseline variables to improve precision and reduce required sample size to achieve desired power.

Continuous Outcomes: Example of Planning Alzheimer's Disease Trial

Context: Vitamin E and Donepezil for the Treatment of Mild Cognitive Impairment (MCI) phase 3 randomized trial (Petersen et al. 2005)

- Primary Outcome Y: Change in Clinical Dementia Rating Sum of Boxes (CDR-SB) at 1.5 years vs. baseline.
- Study arms A: new drug vs. placebo.
- Baseline variables B: age, gender, Alzheimer's Disease Assessment Scale (ADAS)-cognitive score, Mini-Mental State Examination (MMSE) score, Activities of Daily Living total score, Global Deterioration scale, and CDR-SB. .

Goal: Estimate Avg. Treatment Effect (Estimand) $E(Y|A=1) - E(Y|A=0)$.

- 23% sample size reduction comparing covariate-adjusted estimator to unadjusted.

Goals of Covariate Adjustment for Marginal Treatment Effect

- **Goal: Estimation of Average Treatment Effect in a Randomized Trial**. Require consistent, interpretable, model-robust estimators.
- **Not Goal:** Estimation of Conditional (within stratum of **baseline variables** B) Treatment Effects, e.g., $E(Y|A=1,B) - E(Y|A=0,B)$.
  Conditional Treatment Effects would be useful to know, but typically require model assumptions (such as logistic regression model) and uninterpretable under model misspecification.
- **Not Goal:** Finding subpopulations who benefit or patient-specific optimal treatment policy. (Also useful goal in its own right.)

Assumptions

We assume:

- Treatment Randomized (A independent of B) by design.
- Participant data vectors (B_i, A_i, Y_i), for $i = 1$ to n, independent, identically distributed draws from unknown distribution P.

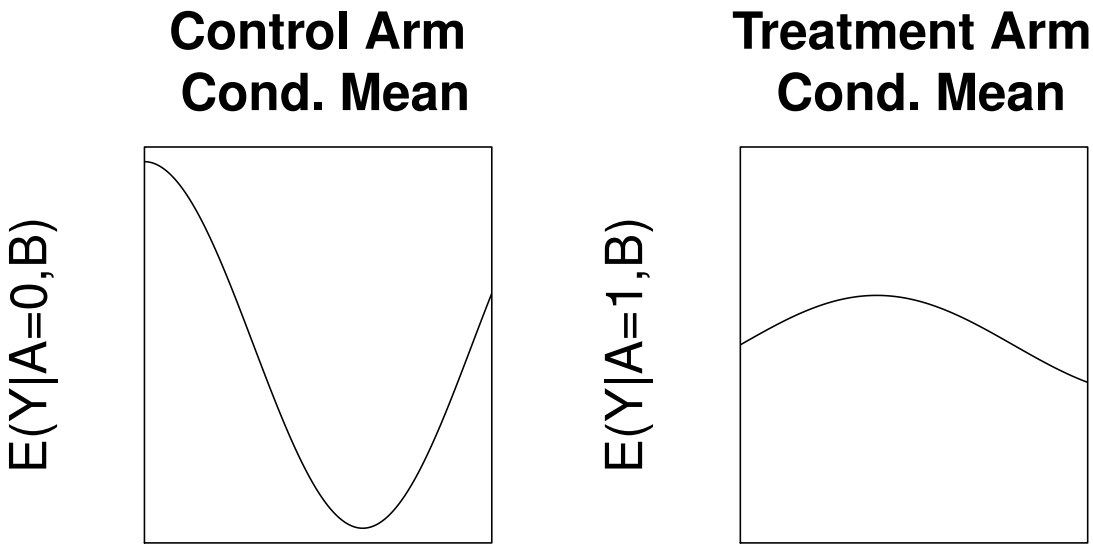
These assumptions (or similar) are needed for standard, unadjusted estimator to be consistent (converge to average treatment effect).

No assumptions on the relationship among B, A, Y except randomization (A, B independent).

We Do Not Make Any Parametric Model Assumptions

- Population distribution of Y given A, B may differ arbitrarily from, e.g., linear regression model $E(Y|A,B) = \beta_0 + \beta_1 A + \beta_2 B$.
- True relationships among B, A, Y may be much more complex than this.
- We require consistent estimators under arbitrary model misspecification.

Hypothetical Example of Misspecification:



Example: ANCOVA estimator for Mean Difference

For continuous Y, to estimate $\mu_1 - \mu_0$ where $\mu_a = E(Y|A = a)$:

- Fit linear regression model $E(Y = 1|A, B) = \beta_0 + \beta_1 A + \beta_2 B$.
- Compute standardized estimators for μ_0, μ_1:
  - $\hat{\mu}_0 = \frac{1}{n}\sum_{i=1}^{n} \hat{\beta}_0 + \hat{\beta}_2 B_i$ (i.e., set $A = 0$ in model fit)
  - $\hat{\mu}_1 = \frac{1}{n}\sum_{i=1}^{n} \hat{\beta}_0 + \hat{\beta}_1 + \hat{\beta}_2 B_i$ (i.e., set $A = 1$ in model fit)
- ANCOVA estimator of $\mu_1 - \mu_0$ is mean difference $\hat{\mu}_1 - \hat{\mu}_0$.

Some remarkable properties of ANCOVA estimator (Yang and Tsiatis, 2001):

- Consistent (converges to average treatment effect) **under arbitrary model misspecification**.
- Equal or better precision (asymptotically) than unadjusted estimator (difference between sample means).

Note: ANCOVA estimator simplifies to $\hat{\beta}_1$, but above construction applies more generally (as shown below).

ANCOVA vs. Unadjusted Estimator Example

TADS Clinical Trial

- Treatment for Adolescents with Depression Study.
- Primary outcome Y: change of Childrens Depression Rating Scale-Revised (CDRS-R) score over 12 weeks.
- Treatment assigment A: Fluoxetine (107) and placebo (112).
- Baseline variables B: baseline CDRS-R score and 8 others on next slide.

ANCOVA Estimator: Impact of each Baseline Variable in TADS trial

Regress outcome (Y=change score) on arm A, baseline vars B:
$E(Y|A,B) = \beta_0 + \beta_A A + \beta_1 B_1 + \cdots + \beta_9 B_9$.
All baseline variables $B_1, \ldots, B_9$ standardized (centered and divided by standard error).

Estimated Coefficients from Regression Model:

ARM	age	sex	CDRS-R	CGI	CGAS	RADS	Suicide ideation	Depr. episode	Comor.
$\hat{\beta}_A$	$\hat{\beta}_1$	$\hat{\beta}_2$	$\hat{\beta}_3$	$\hat{\beta}_4$	$\hat{\beta}_5$	$\hat{\beta}_6$	$\hat{\beta}_7$	$\hat{\beta}_8$	$\hat{\beta}_9$
-4.4	1.5	-0.1	-8.0	-0.6	0.1	-1.0	-1.6	0.8	-0.4

Estimator of average treatment effect is $\hat{\beta}_A = -4.4$.

Clinical Trial Applications

Trial Name	Unadjusted Estimator (95% CI)	ANCOVA Estimator (95% CI)	Impact of Adjustment	Variance Reduction ($\hat{R}^2$)
TADS	-1.4 (-6.0, 3.1)	-4.4 (-8.1, -0.7)	-2.9	32%

Table: Summary of clinical trial data analyses. Negative estimates are in direction of treatment benefit. Variance reduction refers to reduction due to adjusting for baseline variables by ANCOVA.

ANCOVA Estimator: Impact of each Baseline Variable in TADS trial

Regress outcome (Y=change score) on arm A, baseline vars B:
$E(Y|A,B) = \beta_0 + \beta_A A + \beta_1 B_1 + \cdots + \beta_9 B_9$.
All baseline variables $B_1, \ldots, B_9$ standardized (centered and divided by standard error).

Estimated Coefficients from Regression Model:

ARM	age	sex	CDRS-R	CGI	CGAS	RADS	Suicide ideation	Depr. episode	Comor.
$\hat{\beta}_A$	$\hat{\beta}_1$	$\hat{\beta}_2$	$\hat{\beta}_3$	$\hat{\beta}_4$	$\hat{\beta}_5$	$\hat{\beta}_6$	$\hat{\beta}_7$	$\hat{\beta}_8$	$\hat{\beta}_9$
-4.4	1.5	-0.1	-8.0	-0.6	0.1	-1.0	-1.6	0.8	-0.4
Imbal. I_j	0.1	0.0	-0.2	-0.3	-0.1	-0.3	-0.2	0.0	-0.2
Correction i.e., $\hat{\beta}_j I_j$	0.1	0	1.9	0.2	0	0.3	0.4	0	0.1

Estimator of average treatment effect is $\hat{\beta}_A = -4.4$.

Binary Outcomes: Example of Planning MISTIE Phase III Stroke Trial

Problem: Confirmatory trial of new surgical treatment for intracerebral hemorrhage (PI: Daniel Hanley).

- Primary Outcome Y: modified Rankin Scale ≤ 3 at 180 days from enrollment.
- Study arms A: surgery vs. standard of care.
- Baseline variables B: NIH Stroke Scale, clot volume, and location.

Goal: Estimate Avg. Treatment Effect
$P(Y = 1|A = 1) - P(Y = 1|A = 0)$.
Simulated trials based on resampling participants from MISTIE Phase II data.

- 38% precision gain from adjusted estimator compared to unadjusted.
- Equivalent to 28% $(1 - \frac{1}{1.38})$ reduction in required sample size.

Binary Outcomes: Estimands

Notation: outcome Y; study arm $A = 0$ (control) and $A = 1$ (treatment).
$\mu_1 = P(Y = 1|A = 1)$ and $\mu_0 = P(Y = 1|A = 0)$.
Estimand (target of inference) is contrast between μ_1, μ_0:

Estimand 1: Risk Difference. Difference between probability of good outcome comparing treatment to control arms, that is, $P(Y = 1 \,|\, A = 1) - P(Y = 1 \,|\, A = 0) = \mu_1 - \mu_0$.

Estimand 2: Relative Risk. Ratio of probability of good outcome comparing treatment to control arms, that is, $P(Y = 1 \,|\, A = 1)/P(Y = 1 \,|\, A = 0) = \mu_1/\mu_0$.

Estimand 3: Odds Ratio. Ratio of odds of good outcome, comparing treatment to control arms, that is, $\{\mu_1/(1-\mu_1)\} \,/\, \{\mu_0/(1-\mu_0)\}$.

Binary Outcomes: Covariate Adjusted Estimators

For dichotomous Y:

- Fit logistic regression model for $P(Y = 1|A, B) = \text{logit}^{-1}(\beta_0 + \beta_1 A + \beta_2 B)$.
- Compute standardized estimators for treatment specific means μ_0, μ_1:
  - $\hat{\mu}_0 = \frac{1}{n}\sum_{i=1}^{n} \text{logit}^{-1}(\hat{\beta}_0 + \hat{\beta}_2 B_i)$
  - $\hat{\mu}_1 = \frac{1}{n}\sum_{i=1}^{n} \text{logit}^{-1}(\hat{\beta}_0 + \hat{\beta}_1 + \hat{\beta}_2 B_i)$
- Estimator is constrast of interest between μ_1, μ_0, e.g., risk difference $\hat{\mu}_1 - \hat{\mu}_0$.

Estimator $\hat{\mu}_1 - \hat{\mu}_0$ consistent **under arbitrary model misspecification** (Scharfstein, Rotnitzky, Robins, 1999; Moore and van der Laan, 2009, Ge et al. 2011).
Same holds for other (unconditional) estimands, e.g., relative risk

Ordinal Outcome: Estimands

Outcome Y; study arm $A = 0$ (control) and $A = 1$ (treatment).

Estimand 1: Difference in means (DIM). For $u(\cdot)$ a pre-specified, real-valued transformation of an outcome, the estimand is defined as:

$$\text{DIM: } E\{u(Y) \,|\, A = 1\} - E\{u(Y) \,|\, A = 0\}.$$

Estimand 2: Mann-Whitney (MW) estimand.

$$\text{MW: } P\left(\widetilde{Y} > Y \middle| \widetilde{A} = 1, A = 0\right) + \frac{1}{2} P\left(\widetilde{Y} = Y \middle| \widetilde{A} = 1, A = 0\right),$$

for (A, Y) and $(\widetilde{A}, \widetilde{Y})$ independent treatment-outcome pairs.

Estimand 3: Log-odds ratio (LOR).

$$\text{LOR: } \frac{1}{K-1} \sum_{j=1}^{K-1} \log \left\{ \frac{\text{odds}(Y \leq j \,|\, A = 1)}{\text{odds}(Y \leq j \,|\, A = 0)} \right\}.$$

Ordinal Outcome: Covariate Adjusted Estimator

Notation: baseline variables $\mathbf{B}$; study arm A; outcome Y.

- First estimate CDF of Y given study arm $A = a$ for each $a \in \{0, 1\}$, and then substitute into desired estimand.
- To estimate CDF for study arm a, **using only data with** $A = a$, we fit proportional odds working model

$$\text{logit}\left\{P(Y \leq j | A = a, \mathbf{B})\right\} = \alpha_j + \boldsymbol{\beta}^\top \mathbf{B},$$

  for each $j = 1, \ldots, K-1$ with parameters $\alpha_1, \ldots, \alpha_{K-1}, \boldsymbol{\beta}$.
- Then estimator of CDF is $\frac{1}{n}\sum_{i=1}^{n} \hat{P}(Y \leq j | A = a, \mathbf{B}_i)$ where sum is over baseline variables $\mathbf{B}_i$ for **all participants** $i = 1, ..., n$ pooled across study arms.
- Estimator consistent and asymptotically normal under arbitrary model misspecification. Also can be generalized to handle outcomes missing at random, and then double robust. We use superpopulation inference framework assuming $(\mathbf{B}_i, A_i, Y_i), i = 1, ..., n$ i.i.d. draws from unknown distribution.

Time-to-Event Outcome: Estimands

Notation: study arm $A = 0$ (control) and $A = 1$ (treatment); T is event time.

Estimand 1: Difference in restricted mean survival times (RMSTs). The RMST is the expected value of a survival time that is truncated at a specified time τ, that is,

$$\text{RMST: } E(\min\{T, \tau\} \mid A = 1) - E(\min\{T, \tau\} \mid A = 0).$$

Estimand 2: Survival probability difference (also called risk difference, RD). Difference between arm-specific probabilities of survival to a specified time t^*, that is,

$$\text{RD: } P(T \leq t^* \mid A = 1) - P(T \leq t^* \mid A = 0).$$

Estimand 3: Relative risk (RR). Ratio of the arm-specific probabilities of survival to a specified time t^*, that is,

$$\text{RR: } \frac{P(T \leq t^* \mid A = 1)}{P(T \leq t^* \mid A = 0)}.$$

Time-to-Event Outcome: Covariate Adjusted Estimators

- Adjusted Kaplan-Meier estimator for survival curves: Moore and van der Laan 2009, Zhang 2014
- Restricted Mean Survival Time: Moore and van der Laan 2009, Diaz et al. 2019
- If assume proportional hazards model (marginally): Lu and Tsiatis et al. 2011.

Time-to-Event Example: Population, Baseline Variables, and Outcomes in COVID-19 context

- Population: hospitalized, COVID-19 positive patients
- Outcomes: intensive care unit (ICU) admission, intubation with ventilation, and death.
- Baseline variables: age, sex, required supplemental oxygen at ED presentation, dyspnea, hypertension, bilateral infiltrates on the chest x-ray

Data Generating Distributions for Simulations (Survival Outcomes)

- Patient data re-sampled with replacement from 500 patients hospitalized at Weill Cornell Medicine New York Presbyterian Hospital prior to March 28, 2020.
- Simulated sample sizes $n = 100$, 200, 500, and 1000.
- Hypothetical treatment variable drawn independent of all other data
- To simulate positive treatment effect: add independent draw from a χ^2 with 4 d.f. to each treatment arm participant's outcome
- Censoring: 5% censored completely at random; censoring time from uniform distribution on $\{1, \ldots, 14\}$.

Results: difference in restricted mean survival times (RMST) 14 days after hospitalization

Table: **Results when treatment effect is 1 day.** n=sample size; RE=relative efficiency (ratio of adjusted vs. unadj. MSE).

n	Estimator	Power	$n \times$MSE	RE
100	Unadjusted	0.09	53.7	1.00
100	Adjusted	0.15	51.0	0.95
200	Unadjusted	0.33	62.7	1.00
200	Adjusted	0.40	56.4	0.90
500	Unadjusted	0.74	72.9	1.00
500	Adjusted	0.82	62.2	0.85
1000	Unadjusted	0.96	76.5	1.00
1000	Adjusted	0.98	63.5	0.83

Data Generating Distributions for Simulations (Ordinal Outcomes)

- Patient data distribution mimicks distribution from hospitalized, COVID-19 positive patients in (CDC COVID-19 Response Team, 2020)
- Ordinal outcome: 1=death; 2=survival with ICU admission; 3=survival without ICU admission.
- Baseline variable: Age category.
- Simulated sample sizes $n = 100$, 200, 500, and 1000.
- Hypothetical treatment variable drawn independent of all other data.
- To simulate positive treatment effect:
  increased P(No ICU admission and survived | age);
  reduced P(ICU admission and survived | age);
  no change to P(death).
- No censoring

R Packages

- Ordinal Outcomes: `R` package, `drord`, https://github.com/benkeser/drord.
- Time-to-Event Outcomes: `R` package `survtmlerct` https://github.com/idiazst/survtmlerct
- Continuous, Binary, Time-to-Event: `R` package `speff2trial` https://cran.r-project.org/web/packages/speff2trial/speff2trial.pdf

Stratified Randomization and Covariate Adjustment

Wang, B., Susukida, R., Mojtabai, R., Masoumeh, A.-E.; and Rosenblum, M. (2019) Model-Robust Inference for Clinical Trials that Improve Precision by Stratified Randomization and Adjustment for Additional Baseline Variables. https://arxiv.org/abs/1910.13954

- Two commonly used methods for improving precision: **stratified randomization and covariate adjustment**.
- Many trials do not fully capitalize on the combined precision gains from these two methods.
- 70% of confirmatory trials use stratified randomization (Lin et al. 2015).
- Gives general formula for variance of estimator (unadjusted and adjusted) under stratified randomization.
- Handles many estimators used to analyze randomized trials: ANCOVA, standardized logistic regression, MMRM, Kaplan-Meier estimator.

Recommendations for Primary Efficacy Analysis

1. **Estimand when the outcome is ordinal.** Recommend: difference between means or the Mann-Whitney estimand. Don't recommend log odds ratios.
2. **Covariate adjustment.** Adjust for prognostic baseline variables to improve precision and power.
    1. Baseline variables should be specified before the trial is started (or selected using prespecified algorithm, e.g., with cross-validation).
3. **Confidence intervals (CI) and hypothesis testing.** Nonparametric bootstrap (BCa), 10000 replicates for CI.
    1. Entire estimation procedure repeated in each replicate data set.
    2. Hypothesis tests: invert confidence interval or use permutation methods (latter especially for smaller sample sizes)

Recommendations for Primary Efficacy Analysis (con't)

1. **Use Information Monitoring**
   1. Final analysis time based on the information accrued (1/estimator variance).
   2. Precision gains from covariate adjustment translate into faster information accrual and shorter trial duration.
2. **Plotting the CDF and the probability mass function (PMF) when the outcome is ordinal.**
   1. Covariate adjusted estimate of the PMF and/or CDF of primary outcome plotted for each study arm.
   2. Pointwise and simultaneous confidence intervals displayed
3. **Missing covariates.** Impute based only on data from those covariates that were observed.
4. **Missing outcomes.** Use doubly robust methods and sensitivity analyses of robustness to assumptions.

Bottom Line: Pros/Cons in Using Covariate Adjustment

- **Pro:** Covariate adjustment as described above gives consistent estimator of average treatment effect (same quantity estimated by unadjusted estimator); does not require parametric model assumptions.
- **Pro:** If baseline variable(s) strongly prognostic for outcome, covariate adjustment can substantially improve precision + power (or reduce sample size) vs. unadjusted estimator.
- **Pro:** Covariate adjustment useful even in large trials; that's where biggest equivalent sample size reduction
- **Con:** Can lose efficiency (at small sample size) if all baseline variables pure noise, but losses small.
  In simulations, 2% loss at sample size 100; $<$ 1% loss at sample size 1000 (Colantuoni and Rosenblum 2015).

Some resources for optimizing trial design and analysis

Available at **http://rosenblum.jhu.edu**:

- Papers and Open-Source Software for Covariate-Adjustment
- Adaptive Enrichment Design Trial Planning/Optimization Software
- FDA short-course video-recording
- Plain Language Document Outlining Advantages and Limitations of Adaptive Enrichment Designs
- Papers with Statistical Methods and Case Studies

Austin, P. C., A. Manca, M. Zwarenstein, D. N. Juurlink, and M. B. Stanbrook (2010). A substantial and confusing variation exists in handling of baseline covariates in randomized controlled trials: a review of trials published in leading medical journals. *Journal of Clinical Epidemiology 63*(2), 142–153.

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