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Covariate Adjustment in Pragmatic Randomized Clinical Trials in Pain Research

Abstract

Covariate adjustment is an issue that should always be considered and discussed in the context of clinical research, since it could impact the outcome(s) and, thus, conclusions arising from a research project.

Problem Statement

Unlike many disease entities, pain is heterogeneous in terms of diagnosis, causation, duration, chronicity, severity, and control. Consequently, it provides a challenge in terms of patient homogeneity in the context of non-pharmacological randomized controlled clinical trials focusing on prevention/treatment. This has significant impact on the design and analytical considerations vis-à-vis covariate adjustment. Further, the pragmatic nature of such trials accentuates covariate adjustment issues since potential participants have concurrent exposure to a wide variety of prevention and treatment modalities. In addition, prior and/or current exposure to other interventions can complicate the analysis approach.

In the context of clinical trials, the following issues should be considered when addressing covariate-related methodological, statistical and analytical issues:

- Timing of covariate adjustment: During study design (e.g. stratifying variables) or during analysis or both
- Covariate selection methodology
- Participant and/or cluster--level covariates and their impact on treatment effect and power in cluster-randomized trials
- Potential exposure to and/or uptake of multiple prevention/treatment modalities leading to: (i) 'involuntary' cross-over and/or (ii) participants randomized in one trial to the control condition might subsequently be randomized to the intervention arm in another trial (particularly applicable in cluster-randomized trials)

In addition, other issues, specific to pain, arise as a result of the following:

- Availability of and accessibility to data (e.g. use of non-pharmacological modalities)
- Opioid tapering, for reasons unrelated to pain reduction, can lead to uncontrolled pain, especially for patients utilizing non-pharmacological interventions

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- Differential uptake of non-pharmacological modalities due to:
  (a) Secular or geographic trends due to variations in popularity across the US
  (b) Word of mouth due to popularity among different groups of patients e.g. Veterans
  (c) Healthcare facility characteristics e.g. enforcement of opioid tapering, strict adherence to ascertainment of past opioid prescriptions prior to new prescription, availability of non-pharmacological modalities
- Availability of other options for delivery of non-pharmacological modalities e.g. community care facilities

Background

Even though the unadjusted comparison of treatment effects in a clinical trial eliminates post-hoc 'fishing' [1], p-value 'shopping' [2] and selection of an adjusted result that 'accentuates the estimate and/or statistical significance of the treatment effect' [3], covariate adjustment to address baseline group imbalances has been encouraged for more than 20 years [2,4]. Further, even though it provides no clear indication whether unadjusted or adjusted analyses should be used, the 2010 updated CONSORT guidelines [5] clearly specify that all adjusted analyses should be *a priori* planned with the reasons for being carried out explicitly outlined. Likewise, the European Medicines Agency provided a detailed document/guideline on adjustment for baseline covariates in clinical trials [6]. Despite this, it appears that not all published RCT reports are following this practice [7, 8].

Published literature shows that covariate adjustment can potentially:

a) Increase precision of the treatment effect estimator and lead to smaller standard errors, and, in turn, increase power [1, 9, 10, and 11]
b) Minimize potential bias in effect size estimates [7]. For certain measures, such as odds ratios, hazard ratios, or standardized effect sizes, the definition of the treatment effect is dependent on the specific set of covariates which is adjusted for. When such measures are used, estimates of treatment effects may be biased unless the covariates included in the analysis align with the covariates used in the definition of the treatment effect.
c) Minimize overestimation of the standard deviation of the (continuous) outcome-accounts for outcome variation and contribution from other prognostic factors [7]

Further, discussion pertaining to the type of covariates that would/should be collected and used to address imbalances in baseline characteristics, has generated interesting insights:

a) Adjustment for variables used in the randomization (stratification) is common practice [3]. Even though there is support for this practice [12], this might need to be carefully considered,

especially if stratifying covariate(s) are not related to the outcome [3]. In multi-site trials site should be adjusted for in models

b) The baseline measure of the outcome should be either used in adjustment or modeled as a response in repeated measures designs [9, 12, 13, 14, 15]

c) Covariate adjustment in cluster-trials might reduce the within-group variance but at the same time increase the between-group variance; this then results in larger treatment effect standard errors and thus precision. [16, 17]

d) Selection of covariates for adjustment should consider information on the correlation of such covariates with outcome(s) as determined in prior and/or published research: if correlation is weak ($\rho < 0.3$), even if statistically significant, this imbalance is not important; if correlation is strong ($\rho > 0.5$) then adjust, regardless of lack or extent of imbalance [3,10]

Recommendations

The review of published literature highlighted the diversity of approaches and methods used in handling covariates, both in the design and/or analysis phase of a trial. In addition, this review helped identify a number of recommendations that could be considered in the design and analysis of clinical trials in pain management.

A. Given the impact of covariate adjustment on precision and statistical power, sample size estimation should aim to incorporate the impact of covariate adjustment when reliable estimation is available

B. Identify covariates and the feasibility of reliably collecting them from their source *a priori*

C. In the analytical plan of cluster randomized trials, consider methods to assess (a) the impact of adjustment on treatment effect precision; (b) the impact of patients receiving other non-protocol interventions, including the intervention they were not randomized to receive

D. Classify covariates based on their intended use:
   i. Primary Outcome analysis adjustment
   ii. Secondary Outcome analysis adjustment
   iii. Prediction Model development
   iv. Sensitivity analysis

Conclusion

Depending on its function (Primary, Secondary or Sensitivity Analyses) covariate-adjusted analysis should be *a priori* specified in the protocol. Model development can utilize covariate adjustment without necessarily pre-specifying in the protocol.

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