Discussion of Biometrics Manuscript # 060521 *"Principal stratification designs to estimate input data missing due to death"*

Frangakis et al. have presented a creative twist to the principal stratification approach in the context of a missing input due to death. For the first part of the paper extending to Section 5, the context is unique with the assumption that the intervention (Z) is 100% effective in preventing death (fully "proctetable"). However, in Section 6, the authors go a long way to making the methodology more generalizable to contexts where the intervention is partially protectable, but which result in more identifiability problems. We now pursue with additional questions the authors' insightful comparison with other contexts, specifically the non-compliance randomized trial context after equation (2) and in Section 6. For both the fully protectable and partially protectable cases, we relate the authors' strategy to the non compliance-randomized trial context to better understand the ramifications of the assumptions. Following Frangakis et al., we make our comparisons of the assumptions in terms of the implications for the principal strata. The authors note that the four principal strata in their context (protectable always-survivors, never-survivors, and defiers) correspond in a one-to-one way to the four principal strata in the non-compliance, randomized trial context (compliers, always-takers, never-takers, and defiers).

Accordingly, the authors' interpretation of Assumptions I, II, and II' in terms of principal strata can be compared to similar interpretations of analogous assumptions in the randomized trial context and corresponding principal strata. These randomized trial assumptions entail an ignorability assumption related to Assumption I, the exclusion restriction, and a monotonicity assumption analogous to Assumptions II or II' depending on the randomized trial design. The authors mention the relationship between the two contexts with respect to types of monotonicity assumptions. We now attempt to elaborate further on these relationships between the two contexts in terms of ignorability, exclusion restriction, and monotonicity assumptions.

Ignorability

The authors' Assumption I [A, P $\perp$ Z | X] may be stronger than the ignorability or randomization assumption in the non-compliance, randomized context, where A occurs after Z and is measured for both levels of S. Randomization implies A(1), A(0), P $\perp$ Z | X , where A(1) and A(0) are what A would potentially be if a subject were assigned to Z=1 or Z=0, respectively (e.g., Angrist et al. (1996)). In the parlance of randomized trials with non-compliance, the ignorability assumption (Assumption I) of the authors appears to say there is no overall ITT effect of the baseline randomization (Z) on outcome (A). However, the ignorability assumption for randomized trials [A(1), A(0), P $\perp$ Z | X] does not imply such a null effect of Z on A. We note that neither ignorability assumption implies a null ITT effect of Z on A within principal strata, which has implications for the ensuing discussion of the exclusion restriction.

Exclusion Restriction

The authors do not assume the exclusion restriction. On the face of it, one may ask if Assumption I implies the exclusion restriction, as defined in Angrist et al. (1996) for the non-compliance randomized trials context. However, under this exclusion restriction assumption, the ITT effects of Z on A equal zero in always- and never-takers (or never- and always-survivors), which is not necessarily true under Assumption I. The ignorability assumption of Angrist et al. (1996) and exclusion restriction with a monotonicity assumption similar to Assumption II is sufficient for identifying the causal effect of treatment in compliers. One may ask if the exclusion restriction would make sense in the authors' context of missing input due to death, where A temporally precedes Z and S.

Monotonicity

We now attempt to elaborate on the authors' relation between Assumption II and monotonicity. Assumption II seems to lead to the converse situation of the Zelen single consent design (Zelen 1990), under which controls do not have access to the randomized treatment, i.e., Pr(S=1 | Z=0)=0. In such cases, the always-takers and defiers do not exist in comparison to the assumed non-existence of the never-survivors and defiers under Assumption II in the authors' context. That is, the protectable and always-survivor principal strata are specified in the authors' case in contrast to the compliers and never-taker principal strata in the Zelen single consent design. Accordingly, the difference between the causal approach of the authors and the causal methods for the single consent design only involves differences between Assumptions I versus the randomization assumption and the exclusion restriction assumption.

The authors emphasize the importance of some type of monotonicity assumption to identify causal effects in their context of missing input due to death. In both the full and partial preventability cases, they assume that defiers do not exist, as is often done in the non-compliance, randomized trials context. Under partial preventability when the never-survivors exist and thus add parameters in need of identification, the authors impose parametric constraints involving covariates in equation 6 to identify the causal effects of interest. The authors note however at the end of Section 5, "The fact that these quantities would be identifiable by our method even without the models in (6) if samples were large enough means that the results should not be sensitive to the particular parametric models, as long as they are flexible." Given this statement, how important are baseline covariates in identifying parameters under a fully parametric approach with partial preventability? It is clear that parametric relationships between P and baseline covariates X are very crucial for identifiability along with parametric distribution assumptions when monotonicity is relaxed (e.g., Rubin 2004; Ten Have et al. 1994).

In the presence of protectables and always- and never-infected in the vaccine context, Gilbert et al. (2003) augment the monotonicity assumption of no defiers with an additional but unidentifiable parametric relationship. Specifically, under the ignorability assumption [A(0), A(1), P $\perp$ Z | X], Gilbert et al. (2003) specify a parametric model relating S(0) to S(1) and A with the logistic function. In the Gilbert case, the log odds ratio parameter corresponding to A is not identifiable. If assumption I were to make sense in the vaccine context, would Assumptions I and II' help preclude the need for such parameterizing such a relationship? Assumption I may not be feasible for the vaccine case, as it would imply that assignment to vaccine has no effect on disease level.

Finally, there are several interesting extensions of the authors' approach in their missing input/death context involving the incorporation of more information. Such information includes time to death (time to S=1 since the intervening factor (Z)) and also multiple measurements of A across time some of which may be observed before S=1. Given the popularity of joint survival/longitudinal outcome approaches and selection models, such extensions of the authors' work may be beneficial in the missing input context.

In summary, the authors' new implementation of the principal stratification approach has generated many interested questions relating to other contexts and also challenges for incorporating additional information that may be helpful in identifying causal relationships between unmeasured and measured variables.

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