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Letter to the Editor

RE: "EFFECT ESTIMATES IN RANDOMIZED TRIALS AND OBSERVATIONAL STUDIES: COMPARING APPLES WITH APPLES"

In a recent issue of the *Journal*, Lodi et al. (1) published a landmark paper that provides excellent guidelines on how causal effect estimates from randomized trials can be compared with such estimates from observational studies. They suggest that investigators first harmonize study protocols ("stage 1") and then follow this with a harmonized data analysis ("stage 2") and sensitivity analyses ("stage 3"). We propose taking the following considerations into account when designing the target trial protocol.

First, in many (nonpragmatic) randomized trials, the study protocol requires regular visits for the study participants. However, in observational studies, this may not necessarily be the case. As has been shown before (2), effect estimates observed under regular clinic visits may differ substantially from estimates observed under irregular visits. This is because seeing a physician at a particular visit can be interpreted as part of the "intervention package," which may be of benefit to a patient. We therefore suggest incorporating visit frequency into the definition of the treatment strategies. For example, the second treatment strategy in Lodi et al.'s paper may be stated as "deferred initiation of antiretroviral therapy within 1 month of second CD4 cell count <350 cells/mm^3 and mandatory clinic visits every 3 months after enrollment, at which decisions about treatment assignment and referral can be made." Violation of the protocol with respect to visit frequency does not necessarily result in censoring but can be addressed by applying g-methods, where one can intervene on visit frequency and analytically "force" patients to return to the clinic as often as required (stage 2). Although this may not yield the causal effect estimate of primary interest, it could serve comparability.

Second, it is not uncommon that secondary outcomes in clinical trials are evaluated among those patients who survived. In this context, it can be challenging to define causal contrasts that both can be identified and are clinically meaningful. In the paper by Lodi et al. (1), secondary endpoints of interest could be mean CD4 cell count or number of unscheduled hospitalizations among those patients who survived (3). The problem in this case is that identification may not necessarily be possible (4), because 1) the population evaluated will potentially be different for different intervention strategies, since survival differs for different interventions, and 2) there might be unmeasured variables that affect both survival and the outcome and may thus cause selection/collider bias when conditioning on survival—for example, if there is a path like "antiretroviral treatment (time t) $\rightarrow$ survival (time t) $\leftarrow$ previous tuberculosis (time $t-1$) $\rightarrow$ CD4 cell count (time $t+1$)."

The above problems can be avoided by intervening on survival, that is, by estimating the expected mean CD4 cell count that would have been observed if no one had actually died. This may be less meaningful from a clinical perspective, however (5). Alternatively, one may choose causal contrasts such as the survivor average causal effect (SACE), which evaluates the outcome only in the subpopulation that would have survived irrespective of which treatment strategy they were assigned to (6, 7). Again, this may not be the causal contrast needed to inform the treatment decision, but it may serve comparability. Another alternative is to define (secondary) composite endpoints in the study protocol that include both mortality and the outcome in survivors. For example, one could use quality-adjusted life years (8) during follow-up to combine mortality and morbidity. In this case, the outcome would be the area under a quality-of-life score curve, with quality of life being set to 0 at the time a patient dies.

It follows that in studies that involve mortality but where survival is not the outcome of interest, the target trial protocol may often benefit from a note on the identification/justification of the causal contrast. Moreover, a sensitivity analysis (stage 3) estimating the SACE might be useful as well.

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Michael Schomaker[1,2], Felicitas Kühne[1], and Uwe Siebert[1,2,3,4,5] (e-mail: michael.schomaker@umit.at)
[1] *Institute of Public Health, Medical Decision Making and Health Technology Assessment, Department of Public Health, Health Services Research, and Health Technology Assessment, UMIT—University for Health Sciences, Medical Informatics and Technology, Hall in Tirol, Austria*
[2] *Centre for Infectious Disease Epidemiology and Research, University of Cape Town, Cape Town, South Africa*
[3] *Center for Health Decision Science, Department of Health Policy and Management, T.H. Chan School of Public Health, Harvard University, Boston, MA*
[4] *Program on Cardiovascular Research, Institute for Technology Assessment and Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA*
[5] *Division of Health Technology Assessment and Bioinformatics, ONCOTYROL—Center for Personalized Cancer Medicine, Innsbruck, Austria*

Editor's note: *In accordance with* Journal *policy, Lodi et al. were asked if they wished to respond to this letter, but they chose not to do so.*

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