

Supplement

Randomized Explanatory Trials: An Update

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This supplement briefly describes the integration of the concept of a randomized explanatory trial (RET) with the concept of experimental therapeutics. The term randomized explanatory trial was first coined by Schwartz and Lellouch (1967) and juxtaposed against what they called pragmatic trials (PTs). Schwartz and Lellouch characterize an RET as a randomized controlled trial (RCT) designed to shed insights on the causal impact of a treatment component on an outcome. By contrast, they state that pragmatic trials (PTs) are designed to compare the relative effectiveness of two or more treatments in practical conditions. Since their seminal paper, the terms explanatory and pragmatic trials have been used in diverse ways in the scientific literature, but the essence of the distinction has focused on a concern for understanding the causal mechanisms underlying the effect of a treatment on an outcome (RET) under idealized experimental conditions on the one hand versus the comparative effects of treatments in practical settings on the other hand.

The importance of pursuing causal analysis in randomized trials (i.e., the conduct of RETs) has recently been emphasized by the National Institute of Mental Health. The director of NIMH, Joshua Gordon, has embraced the concept of experimental therapeutics (ETs) as central to the NIMH mission and has incorporated ETs as a formal part of the NIMH Strategic Plan for Research (Gordon, 2017). The ET approach seeks to translate the “the growing understanding of the factors that cause and sustain mental illnesses into new or improved approaches to prevention and treatment...and to suggest malleable targets (and potential mediators) for novel intervention strategies” (Gordon, 2017). Gordon also notes that “evaluating the relationship between changes in these targets or mediators and changes in symptoms allows us to fine-tune our understanding of mental illness and helps us prioritize the most promising interventions for further investment. Consideration of these factors enables research aimed at refining therapies to increase potency

and efficiency, and personalizing interventions to ensure that they are optimally matched to individual needs.”

Flash forward some fifty years since the seminal paper by Schwartz and Lellouch and it is clear that the concept of an RET has evolved considerably since its introduction in 1967, both conceptually and methodologically. To be sure, the essence of a randomized explanatory trial remains that of understanding the causal mechanisms that account for the effects of treatments on outcomes, but RETs have evolved to include the core concepts of mediation and moderation in conjunction with far more advanced conceptual, psychometric, and methodological tools than when Schwartz and Lellouch first coined the term and juxtaposed RETs with PTs. Our article, in part, serves as an (albeit brief) updating of the RET concept. It broadens the notion of an RET to include a larger frame of modern scientific activities/constructs that span (a) qualitative/participatory and quantitative methods, (b) mediation and moderation, (c) feasibility and full-fledged trial designs, and (d) state-of-the art analytic methods, all focused on translating and extending causal theories of factors that impact mental health outcomes into viable, practical, and personalized treatment protocols.

We take the RET concept a step further than the above, however, by also arguing that the dichotomization of trials into RETs versus PTs as being somewhat counterproductive. To be sure, we fully recognize, as does NIMH, the unique influences on outcomes that are relevant in practical, real-life contexts. However, PTs morph or blend into RETs when we seek to understand the nature of those unique influences and to formally address them in our interventions and intervention roll-outs in applied contexts. It no longer is enough to document the effectiveness rates of a treatment in an applied context or to demonstrate that one treatment works better than another treatment in an applied context. This is too narrow a perspective.

Instead, we need to know *why* one treatment works better than another treatment in applied contexts, *why* a treatment fails or succeeds in an applied context, and for whom this is and is not the case. In other words, PTs need to incorporate RET perspectives that elucidate mediators and moderators that operate in applied contexts and that make use of modern scientific tools and methods to help us understand and improve intervention impact. The focus should not only be on testing whether interventions work in applied contexts, but also on understanding why they work (or do not work) in those contexts and whether intervention effects operate through the presumed mechanisms of influence whether those mechanisms are basic or unique to a given type of applied context. Our article is a small step in prioritizing this direction for the field.

References

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- Schwartz, D. & Lellouch, J. (1967). Explanatory and pragmatic attitudes in therapeutical trials, *Journal of Chronic Diseases*, 20 (8), 637–648.