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Short Communication

# The Importance of Measuring Indirect Treatment Effects

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## Introduction

The current FDA model of drug approval relies on determining the direct effect of treatment on outcomes of interest, including an evaluation of patient experience. The Cures Act (among others) that amends the Federal Foods and Cosmetic Act defines patient experience data as:

> "data that are collected by any persons (including patients, family members, and caregivers of patients, patient advocacy organizations, disease research foundations, researchers, and drug manufacturers); and are intended to provide information about patients' experiences with a disease or condition, including (A) the impact (including physical and psychosocial impacts) of such disease or condition, or a related therapy or clinical investigation, on patients' lives; and (B) patient preferences with respect to treatment of such disease or condition.
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> "(source:https://www.fda.gov/drugs/development-approval-process-drugs/cder-patient-focused-drug-development; https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical).

Patient experience can be documented using different research vehicles, such as Clinical Outcome Assessments (COAs), qualitative studies, and observational prospective studies that capture the patient experience.

The types of research vehicles are displayed in table 1, below. Though there is considerable flexibility in the type of study that can be designed to capture patient experience data, it is preferable that the design is discussed with the FDA prior to execution. This will help ensure alignment with FDA on patient experience endpoints and study design.

Clinical trials usually analyze the effect of treatment using measures that describe the signs (experience of the disease by the patient noted by clinicians) and symptoms (experience of the disease by the patient noted by patients) and subsequently the effect of treatment on the severity of the disease. Consideration is generally given to the impacts of the disease on the functional and psychosocial domains of patient experience. It is interesting that these two domains are downstream from the initial effect of treatment (i.e., on signs and symptoms of the disease), and are thus often subject to mediation effects and its bias. Further, when clinicians are asked about how they view any new treatment modality, they usually list two requirements: the effect of the new treatment on the signs/symptoms, and the effect of a change in the signs/symptoms on either the functional or psychosocial domain. The latter part of the health care practitioner (HCP) evaluation focuses itself on the indirect effect of treatment on outcomes, which is seldom analyzed correctly with clinical trial data.

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|---|---|
| ***Clinical Outcome Assessments***: | ***Clinical reported outcomes (ClinRO)*** - A measurement based on the report from the healthcare provider<br>***Patient reported outcomes (PRO)*** - A measurement based on the report from the patient, themselves<br>***Observer reported outcomes (ObsRO)*** - A measurement based on the report from someone other than the healthcare provider or patient<br>***Performance based outcome (PerfO)*** - A measurement based on the report from standardized task performed by the patient |
| ***Qualitative studies***: | Patient/Caregiver Interviews<br>Focus group/Expert Panel, etc |
| Patient focused drug development or other stakeholder meeting reports | |
| Observational survey studies designed to capture patient experience data | |
| Natural History Studies | |
| Patient Preference Studies | |

***Source:*** ERG,"Assessment of the use of Patient Experience data in the regulatory process", Final report 2021.

***Table 1:*** Patient Experience Data accepted by the FDA.

The effect of treatment on an outcome variable is termed a direct effect of treatment, while an indirect effect refers to the effect of treatment via an intermediary variable on the outcome. By considering direct and indirect effects, the HCP can understand the full effect of the new treatment modality. This view is never considered when submitting evidence to the regulatory authorities or generating clinical trial evidence. For example, an exploratory endpoint in a clinical trial may be to examine the effect of treatment on global health or quality of life, but the analyses will treat this as a direct effect without considering intervening symptoms, such as changes in pain or fatigue that would then have downstream effects on quality of life. Further, "A problem associated with the estimation of direct effects….. is what we call intermediate variable bias, which is attributable to intermediate confounders—or variables that are affected by the treatment and affect both the mediator and outcome". (Acharya, 2016) Given, the interest of HCPs in understanding the effect of the mediation variables on outcome, it necessitates the idea of estimating the indirect effect. For example, the influence of a treatment effect on function, can be dissected into the direct effect of treatment and the indirect effect of treatment mediated, say via signs and symptoms of the disease. That is, treatment reduces pain and the reduction in pain increases function. This type of relationship can be shown in the diagram below (note: that the dash and orange arrows represent possible indirect effects, while the solid bluearrows represent the direct effects. For simplicity, not all indirect effects are presented).

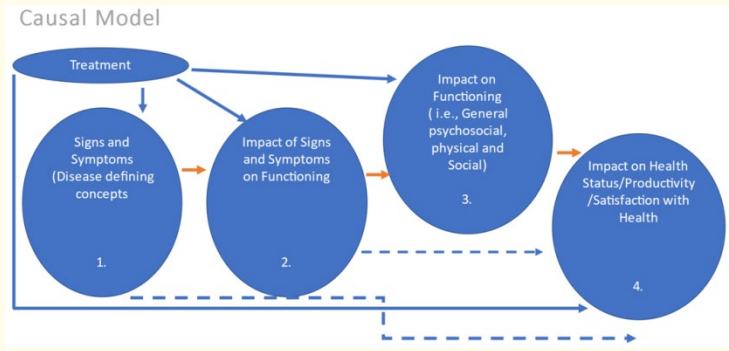


***Figure 1:*** Causal model.

In this casual model, treatment can be seen influencing the signs and symptoms of the disease and its effect on health status mediated by impact of signs and symptoms on functioning; and impact on functioning). The measurement of the indirect effect can be useful when discussing the effects of treatment on outcomes. The discussion can center around the direct effect of treatment on outcomes and the mediated effect of treatment on outcomes. This provides a much more complete assessment of the true treatment effect on different outcomes.

One method of addressing these models, a two-stage estimation approach known as the sequential g-estimator, has been proposed to eliminate the influence of the mediator variable on the outcome. (Acharya, 2016). The important point here is that the direct effect can be biased even when attempting to control for other variables. A problem with the sequential g-estimator approach is that it discards important information in the process of generating a "de-mediated" effect of treatment on outcome. An alternative method that can handle multiple direct and indirect effects simultaneously is structural equation modeling (SEM). SEM has been used to assess complex direct and indirect relationships among symptoms, patient functioning, and global health status/quality of life (GHS/QOL) with data from oncology trials examining the EORTC QLQ-C30 (Stull et al., 2017). These methods yield a decomposition of total effects of treatment on more distal outcomes into direct and indirect effects. Direct effects of treatment on these distal outcomes may be trivial and non-significant, but the indirect effects may be significant. Thus, in these circumstances, standard regression or MMRM analyses would not yield empirical support for the hypothesis that treatment affects GHS/QOL, whereas SEM would allow for proper tests of these relationships.

In conclusion, because functional and psychosocial variables as well as GHS/QOL (e.g., as determined from health-related quality of life measures such as the EQ5D5L, SF-36, or EORTC QLQ-C30) are measures that are more distal from the initial effect of treatment, an examination of the indirect effects is warranted.

## References

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