What is an estimand in a clinical trial: The PIONEER 1 example

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Video Abstract

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Abstract

To create safe and effective treatment plans, prescribing physicians and their patients must understand the effects of a medication. Clinical trials provide descriptions of those effects. But these descriptions can be complicated by the many different ways data are analyzed and interpreted in clinical trials. Specifically, [intercurrent events], events that occur after treatment initiation, can affect interpretation. How can researchers account for these events? By baking them into their research question before their study even begins. That's the goal behind the use of estimands. An estimand is a detailed description of the [treatment effect] estimated to address a scientific question of interest. As such, estimands ensure that study objectives align with the design, conduct, and analysis of a trial. And more than one estimand can be defined for the same endpoint. To illustrate how estimands work, consider the PIONEER 1 clinical trial. PIONEER 1 investigated the efficacy and safety of oral semaglutide versus placebo in adult patients with type 2 diabetes. The trial sought to answer two questions: What is the treatment effect in the target population regardless of trial product discontinuation or use of rescue medication? And what would the treatment effect have been had all patients remained on the trial product and not used rescue medication? Each question was addressed using a precisely defined estimand: the [treatment policy estimand], defined as the difference between treatments in change from baseline to week 26 in HbA1c and body weight regardless of trial product discontinuation and/or addition of rescue medication; and the [trial product estimand], also evaluating the difference in HbA1c and body weight, but assuming all patients had remained on trial product for the entire trial without rescue medication. While the two estimands addressed two different questions, both add to the full clinical picture provided by PIONEER 1. For example, with the highest dose of oral semaglutide tested, the estimated treatment differences in HbA1c and body weight versus placebo according to the [trial product estimand] were slightly greater than those estimated by the [treatment policy estimand]. For HbA1c, the difference was likely a reflection of the increased use of rescue medication in the placebo group. For body weight, because oral semaglutide is known to cause greater weight loss than other glucose-lowering agents, prematurely discontinuing the medication would unlikely result in the same weight-loss experience. That likely accounts for the smaller difference in weight change estimated by the [treatment policy estimand]. Understanding how and why estimands are used is important. It could help both clinicians and regulators evaluate treatment effects from different perspectives. In the context of diabetes treatment and beyond, estimands provide clarity in interpreting and comparing trial results and appropriately guiding clinical decisions.