Evolution Research Group

From the Desk of the CSO
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Placebo Hygiene in the GLP-1 ERA:
When Placebo Participants Find Active Treatment

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A finding in the recently published Phase 3 SYNCHRONIZE-1 trial of survodutide caught my attention for a reason that extends beyond the efficacy of the investigational drug.

KEY OBSERVATION

16.5% of placebo participants reported using another medication with GLP-1 receptor agonist activity.

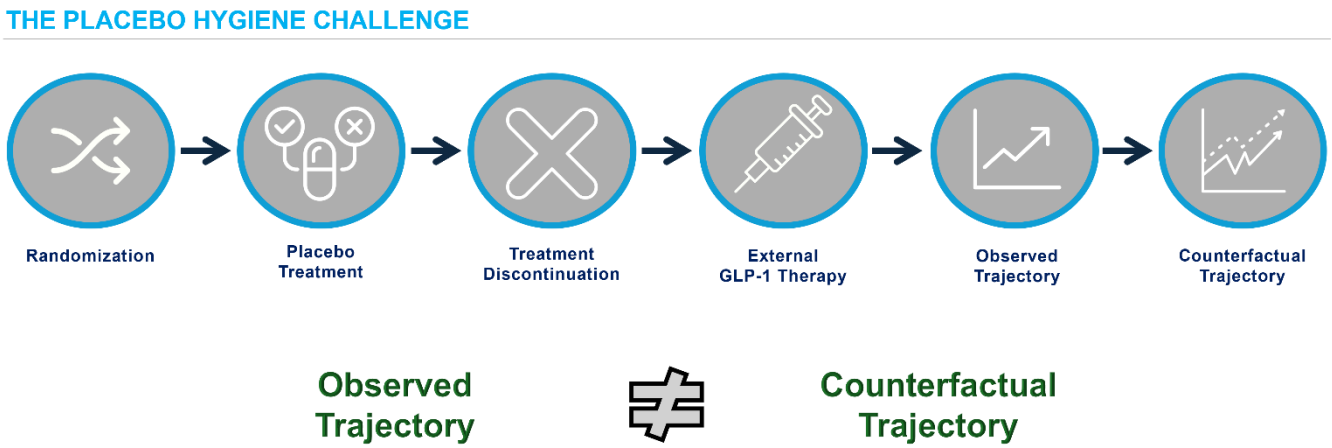
vs.

2.5% | **3.7%** of participants in the two survodutide groups

Use occurred most commonly after participants discontinued assigned study treatment.[1]

Although other obesity medications were prohibited by the protocol, 16.5% of participants randomized to placebo reported using another medication with GLP-1 receptor agonist activity during the trial. By comparison, this occurred in only 2.5% and 3.7% of participants in the two survodutide groups. Across treatment groups, use of another GLP-1 receptor agonist occurred most commonly after participants discontinued assigned study treatment.[1]

This illustrates an emerging challenge that I think of as placebo hygiene.



The placebo group lost an estimated 5.4% of baseline body weight under the trial's treatment-regimen estimand, considerably more than the 2% to 3% anticipated by the investigators. The authors specifically noted that this unexpectedly large placebo response may have reflected participant access to approved or compounded obesity medications.[1] Under a separate efficacy estimand, which estimated the hypothetical effect if participants adhered to assigned treatment and not received prohibited obesity therapy, estimated placebo weight loss was 3.2%.[1]

Importantly, the difference between these estimates cannot be attributed specifically to prohibited GLP-1 use. The two estimands handle multiple intercurrent events differently, including treatment discontinuation, and the authors noted that discontinuation most likely contributed substantially to their divergence.[1] What the trial demonstrates more clearly is the underlying methodological problem: in today's therapeutic environment, participants randomized to placebo may discontinue assigned treatment and subsequently obtain highly effective obesity therapy outside the protocol.

As these therapies become increasingly accessible, that problem may become more consequential. A participant who perceives inadequate benefit from placebo can discontinue study treatment and initiate alternative therapy, materially changing the subsequent weight trajectory. We can observe that new trajectory, but we cannot directly observe what would have happened to that same participant had prohibited therapy never been initiated.

That distinction is important.

> **The problem is not always that the outcome is missing. The problem may be that the outcome we observe is no longer the outcome required by the scientific question.**



ERG RESEARCH PERSPECTIVE

At ERG, we are interested in this challenge from both an operational and a scientific perspective. In addition to executing obesity trials across our network, we have an ongoing research program evaluating whether individualized digital twins can help reconstruct counterfactual longitudinal trajectories following treatment discontinuation and other intercurrent events. Our work is examining these approaches alongside conventional methods such as mixed models for repeated measures and multiple imputation, with the goal of understanding where digital twin methods may provide useful estimand-aligned sensitivity analyses rather than replacing established statistical approaches.[2,3]

This work has progressed from simulation-based methodological research, including an abstract accepted for presentation at ObesityWeek, and has informed a proposed broader precompetitive initiative exploring retrospective and prospective validation using clinical trial data.[2,3] Digital twins are also being investigated more broadly as individualized predictive tools with potential applications across randomized clinical trials and model-informed drug development.[4]

SYNCHRONIZE-1 therefore raises a question that may become increasingly

important for obesity drug development:

THE QUESTION AHEAD

As effective obesity therapies become easier for trial participants to obtain outside the protocol, how do we preserve placebo integrity and accurately estimate the treatment effect that would have been observed without that external therapeutic influence?



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