

Strategies in Anti-Obesity Medication Clinical Trials: Addressing Drop Out Rate and Improving Retention

INCRETIN-BASED ANTI-OBESITY MEDICATIONS (AOMs) represent a therapeutic revolution in the pharmacologic management of chronic weight, producing substantial and sustained weight loss while also improving glycemic control, cardiometabolic risk factors, and cardiovascular outcomes. These medications also reduce food cravings, "food noise," and addictive eating behaviors.

Despite their therapeutic promise, clinical trials of anti-obesity medications have historically experienced relatively high rates of treatment discontinuation. Attrition rates of approximately 15-30% have been reported in major Phase III programs such as the STEP (semaglutide) and SURMOUNT (tirzepatide) trials. In the SELECT trial of semaglutide 2.4 mg, premature discontinuation occurred in 26.7% of participants receiving semaglutide versus 23.6% receiving placebo, with adverse events, particularly gastrointestinal events, being a major contributor. Such drop-out rates can limit drug exposure, reduce statistical power, and introduce bias into efficacy and safety analyses. Importantly, ICH E9(R1) recognizes treatment discontinuation as a key intercurrent event that must be carefully addressed in study design, analysis, and interpretation to preserve the scientific validity of clinical trials.

The purpose of this white paper is to explore the factors contributing to participant drop-out in AOM clinical trials and to describe patient-centered strategies that can improve retention. Building on Signant Health's approach to

ABOUT THE AUTHORS

MARCELA ROY, MA, executive director, clinical (science & medicine); **LAUREN CROOKS, MSc,** associate director, clinical; **GRAHAM ELLIS, MD,** clinical vice president; **ALAN KOTT, MUDR,** practice lead, data analytics; **DAWIE WESSELS, MD,** chief medical officer; **ELIAS KETIAR, MD, MRCP,** clinical vice president; all with Signant Health

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participant support, the paper outlines practical methods to enhance engagement, promote adherence, and ensure more robust evaluation of emerging therapies.

Understanding the scope of attrition in AOM trials

People living with obesity (PLWO) face multiple barriers to sustained engagement in AOM trials. Gastrointestinal adverse events are the commonest cause of drop-outs in incretin-based trials (e.g. 4-7% in SURMOUNT-1/Tirzepatide). They are dose-related and tend to diminish as patients develop tolerance. Early discontinuation is, however, multifactorial and other common causes include:

- **Perceived lack of efficacy:** Failure to lose weight due to placebo treatment, non-responders or subtherapeutic dose is a major risk in longer placebo controlled (Phase III) trials. The availability of approved AOMs and competitive trials may compound the risk of dropouts in patients in whom their weight loss falls short of their expectations.
- **Logistical or trial burden:** Patient preference for oral medications over injectable formulations, in-clinic visit demands, high logistical burden, and long duration trials impose a mismatch between patient expectations and clinical reality.
- **Perceived excessive weight loss:** Emerging incretin-based therapies can produce very large weight reductions. Patients who experience very large, rapid weight losses early on (with >10% weight loss at 1 month) have been shown to be at increased likelihood of dropout compared to the reference group (Talay et al., 2025).

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Evidence-based strategies for improving retention

FINDINGS FROM SYSTEMATIC REVIEW EVIDENCE

A systematic review by Pirotta et al. (2019) examined weight loss interventions across 57 studies with over 7,500 participants. Three approaches showed particularly robust effects: financial incentives reduced the risk of attrition by up to 43%; self-monitoring interventions reduced attrition risk by 41%; and multicomponent interventions combining nutrition support, physical activity guidance, and psychological assistance reduced attrition by 33%. Consistent with FDA 2025 recommendations, at least one Phase III trial should integrate

a standardized, scalable lifestyle-modification program alongside pharmacotherapy.

EVIDENCE FROM DIETITIAN SUPPORT PROGRAMS

Structured support systems for study dietitians are effective in maintaining patient engagement. Dietitian support programs achieved an impressive 82% median 1-year retention rate in a study with 4,410 participants across 15 countries in Phase III trials, with reduced drop-out rates by 32% (after a minimum of 11 teleconferences attended) (Delahanty et al., 2016).

EMPIRICAL VALIDATION FROM LARGE-SCALE IMPLEMENTATION

Signant Health's expertise is built on supporting over 37 GLP-1 protocols across more than 35 countries, leading to 3 new regulatory drug approvals. Implementation of large-scale Phase III obesity programs involved 17,500 participants across 640+ research sites. Study visit attendance averaged 93.4% across AOM trials, markedly higher than the mean reported in published meta-analyses. Home-based visit compliance averaged 72%, approximately 7% greater than the average of 65% across long-term trials. When patients feel supported, informed, and engaged through tools that reduce trial participation burden, they demonstrate good compliance rates.

Goal setting is key in behavioral engagement and retention

A comprehensive review of 24 studies including 21 randomized controlled trials (2016-2025) with over 5,000 participants examined the effectiveness of goal-setting interventions for weight, diet, or physical activity (Crooks et al., 2025). Goal-setting interventions more consistently improved behavioral outcomes than weight outcomes, with several trials demonstrating behavioral improvements without corresponding weight changes, suggesting that goal-setting's primary mechanism operates through behavior modification that may precede or occur independently of weight change.

Key findings on optimal implementation strategies include:

- **Adaptive goals** consistently outperformed static targets, adjusting based on individual progress and relative performance.
- **Dietary goals** demonstrated substantially higher improvement rates (71%) compared with weight-loss goals (39%), suggesting that focusing on controllable behaviors produces stronger engagement and adherence.
- **Coping-planning modules** increased active minutes when goal-setting alone did not. The combination of goal-setting with explicit strategies for overcoming barriers enhanced the translation of intentions into actual behavior change.
- **High weekly engagement** yielded the strongest effects on both weight and HbA1c. Structured weekly engagement should extend beyond six months to produce sustained behavioral change.

Behavioral goal achievement should be tracked independently from weight outcomes. Since goal-setting more reliably influences behavior than weight, monitoring behavioral goal attainment provides an early indicator of intervention engagement and potential efficacy, while also offering opportunities for intervention adjustment before weight outcomes fully manifest.

Moving toward predictive, data-driven engagement

The future of obesity trial retention lies in predictive approaches that identify at-risk patients before discontinuation occurs. Predictive analytics enable targeted intervention by analyzing ePRO metadata patterns (completion rates, timing trends, response delays) in combination with clinical data (weight loss trajectories, visit history, titration patterns) to generate real-time risk stratification and trigger targeted support interventions.

Advanced analytical approaches applied to longitudinal eCOA and digital engagement data may help distinguish patients whose dropout risk is primarily driven by perceived lack of efficacy from those affected by other barriers (e.g., tolerability, logistics, psychosocial factors). By integrating early weight loss data with engagement metrics, site staff can define prespecified thresholds that trigger timely outreach to proactively address concerns about treatment effectiveness and provide personalized encouragement based on objective evidence of clinical response (Johnson et al., 2026).

Comprehensive prevention strategies: A systematic approach

Addressing patient attrition in AOM trials requires systematic intervention across multiple trial phases. Effective prevention combines technological solutions with process improvements and behavioral interventions. Patient education about the physical, behavioral, and emotional impacts of AOMs is essential-patients must understand what to expect during dose escalation, the timeline for therapeutic response, and the importance of persistence through initial side effects. Site staff training to recognize and address obesity bias ensures that patients are respected and supported throughout trial participation.

Patient-centric digital solutions, including intuitive electronic data capture systems, telehealth capabilities, visit schedule modules, and real-time compliance monitoring, can substantially improve retention by reducing participant burden and enabling remote participation. The FDA 2025

guidance expands safety monitoring requirements to include comprehensive cardiovascular assessment, neuropsychiatric evaluation, immunogenicity testing, and abuse liability assessment, making engagement strategies essential not only for efficacy measurement but also for adequate safety characterization.

Mental health monitoring is also an essential component of obesity trial safety assessment. The 2025 FDA obesity guidance explicitly recommends structured neuropsychiatric safety assessment for centrally acting weight-reduction drugs, supporting the routine use of instruments such as the PHQ-9 and C-SSRS. Site staff must be trained to administer these assessments in a supportive manner that reinforces participants' sense of being cared for rather than creating additional burden or anxiety.

The path forward

The path forward for obesity trial sponsors is to make patient retention, data quality, and equity the organizing principles of trial design from the outset, rather than afterthoughts addressed only after dropout is already underway. Reactive problem-solving is insufficient given what the evidence now supports. An analytics-driven operating model that anticipates discontinuation risk and standardizes best practices at scale is both achievable and necessary.

In practice, this means continuous, centralized, and actionable data quality monitoring; integrating real-time oversight across ePRO, EDC, and visit-tracking systems, with automated alerts for missing data, protocol deviations, and aberrant values. It means embedding risk stratification and predictive analytics into routine trial operations, identifying participants at higher risk for dropout and triggering tiered support pathways before disengagement progresses to withdrawal. It means treating patient retention as a designed outcome, supported by standardized engagement packages that combine adaptive goal setting, dietitian and site support, and flexible visit options. And it means systematically reducing bias and enhancing standardization through harmonized training, standardized digital workflows, and analytic checks for differential engagement across demographic subgroups.

Given that there is currently no evidence that PLWO will remain engaged for the full trial duration or will be able to access AOMs following study completion, implementing robust patient engagement strategies is not optional. The question is no longer whether we can solve this problem-the evidence demonstrates that we have both the understanding and the tools to transform patient retention in obesity trials. The imperative now is to implement these proven solutions rapidly and systematically across the industry.

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