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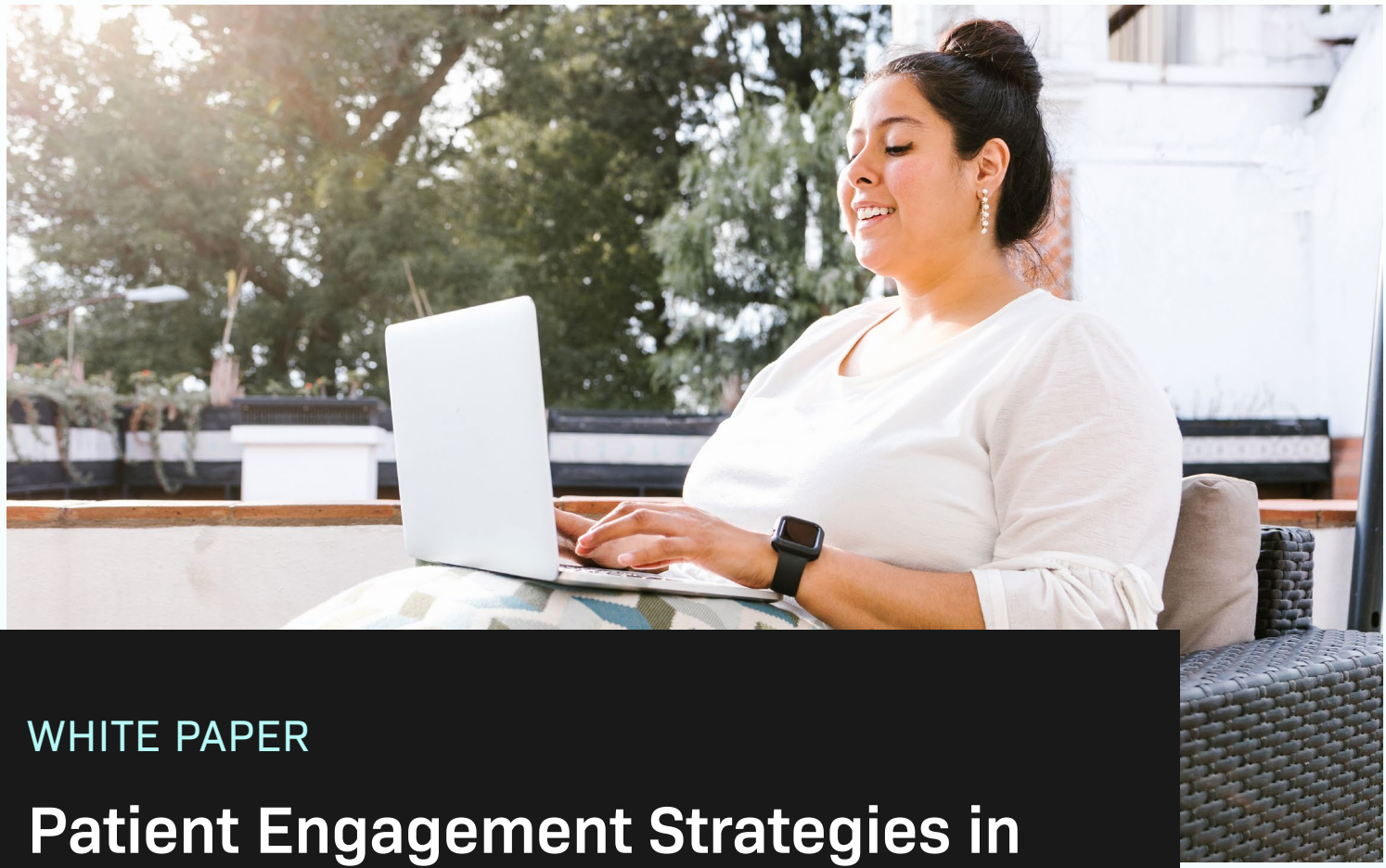

WHITE PAPER

Patient Engagement Strategies in Anti-obesity Medication Clinical Trials: Addressing Drop Out Rate and Improving Retention

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Introduction

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 glycaemic 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.

Addressing these challenges requires a greater focus on patient-centered trial design and engagement strategies aimed at improving adherence, minimizing attrition, and ensuring robust evaluation of emerging therapies. Attrition rates of approximately 15-30% have been reported in major Phase 3 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 to treatment.

Importantly, treatment discontinuation is not unique to incretin-based AOMs; in a recently published Phase 2 trial evaluating bimagrumab alone or in combination with semaglutide (March 2026), adverse-event–related discontinuations occurred in 14.0–21.4% of participants receiving bimagrumab compared with 3.6–8.8% with semaglutide, 5.3–12.5% with combination therapy, and 3.6% with placebo.

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

Evidence-based strategies for improving retention

People living with obesity (PLWO) face multiple barriers to sustained engagement in AOM trials. These challenges manifest through several interconnected mechanisms that reflect the inherent pressures within both the clinical condition, clinical research, and socioeconomic environment. Gastrointestinal adverse events are the most common 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 (Jastreboff et al., 2024).

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 3) 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.

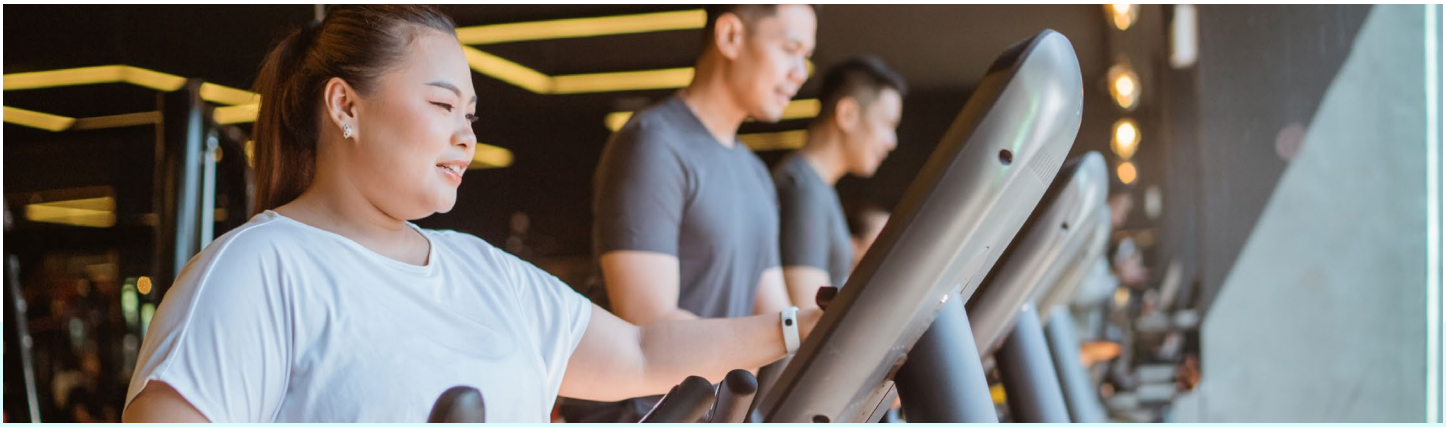
Logistical or trial burden

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, and recent trials have reported small numbers of discontinuations associated with excessive or undesired weight loss as was noted in the Phase 2 retatrutide trial (Jastreboff et al., 2023). 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).

Together, these factors may lead to behavioral disengagement, loss of motivation, reduced study and treatment compliance, and ultimately, early treatment termination and dropout.



Evidence-based strategies for improving retention

Recognizing that traditional approaches to patient retention inadequately address the systematic challenges in AOM trials, researchers have systematically evaluated which engagement strategies produce measurable improvements in retention rates. The evidence base now provides clear guidance on effective interventions.

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 to identify the effects of specific intervention strategies on attrition. The analysis revealed three approaches with particularly robust effects:

1. Financial incentives reduced the risk of attrition by up to 43%. This finding suggests that addressing the opportunity costs associated with trial participation through appropriate compensation can meaningfully influence retention decisions.
2. Self-monitoring interventions reduced attrition risk by 41%. This approach potentially employs increased patient awareness of their own progress, enhanced sense of control over treatment outcomes, and regular engagement with trial-related activities that maintain connection to the study protocol.
3. Multicomponent interventions combining nutrition support, physical activity guidance, and psychological assistance reduced attrition by 33%. The integrated nature of these programs addresses multiple dimensions of the obesity treatment experience simultaneously, providing comprehensive support that mirrors the multifactorial nature of the condition itself. Consistent with FDA 2025 recommendations, at least one Phase 3 trial should integrate a standardized, scalable lifestyle-modification program alongside pharmacotherapy, mirroring what is feasible in routine primary care (FDA, 2025).

Evidence from dietician support programs

Nutrition and lifestyle-based support is particularly important for patients who do not achieve clinically meaningful weight loss, as this group is at higher risk of discontinuing treatment due to perceived lack of efficacy or demotivation. In these individuals, structured behavioral support can help maintain engagement, reinforce adherence to the trial protocol, and sustain healthy behaviors even in the absence of rapid weight change.

Additional research has demonstrated that 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 3 trials. Further analysis revealed that dietitian support programs led to reduced drop-out rates by 32% (after a minimum of 11 teleconferences attended) (Delahanty et al., 2016).

These findings suggest that regular, structured contact with qualified healthcare professionals collaborating with dietitians provides practical guidance that strengthens patient commitment to trial participation.

Empirical validation from large-scale implementation

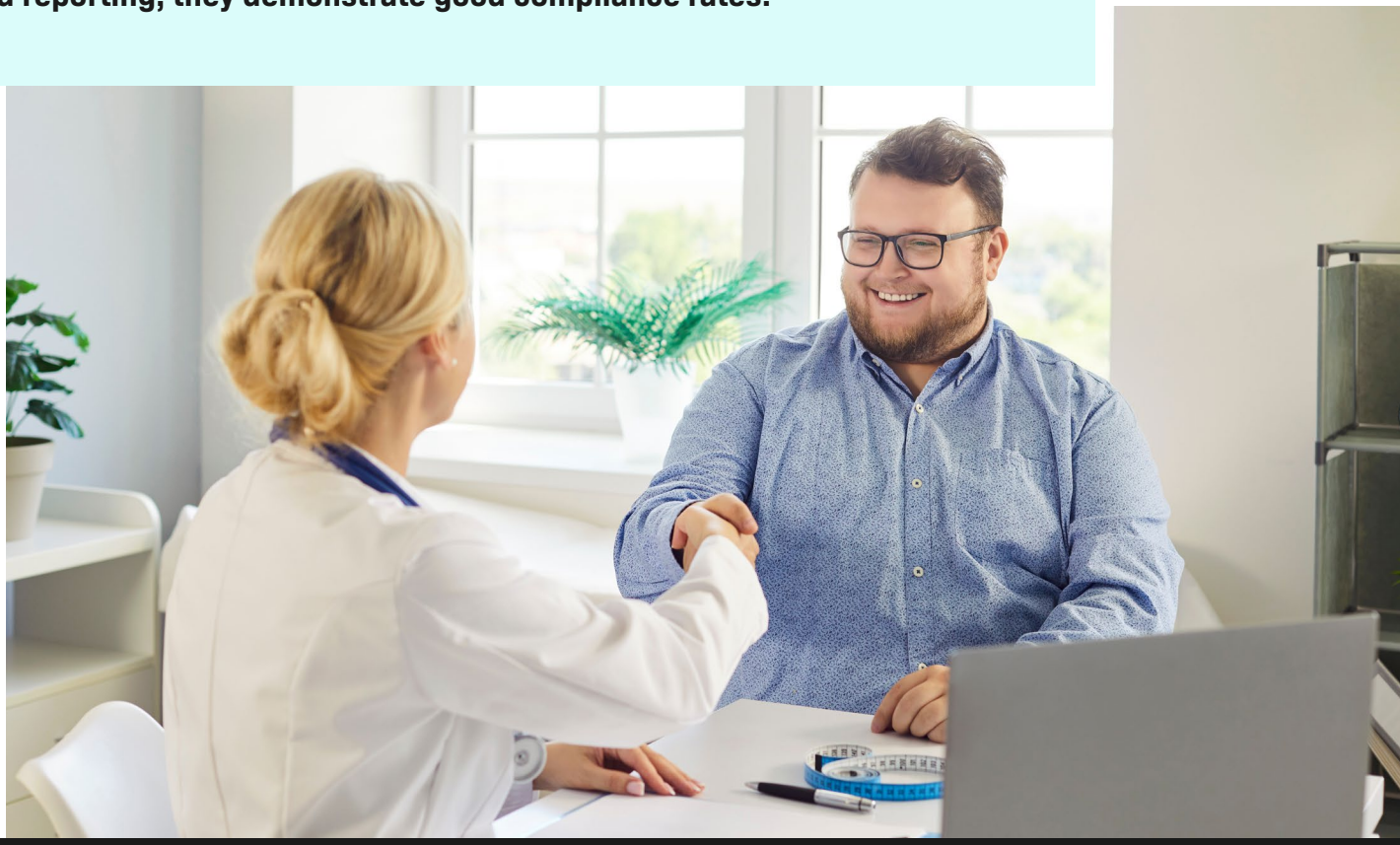
Signant Health's expertise in AOM clinical trials is built on substantial experience of supporting over 37 GLP-1 protocols across more than 35 countries, leading to 3 new regulatory drug approvals. The implementation of large-scale Phase III obesity programs supporting FDA approval has involved 17,500 participants across 640+ research sites, with durations often exceeding three years.

The impact of Signant's support programs demonstrated high levels of compliance:

1. Study visit attendance averaged 93.4% across AOM trials. This elevated level of visit attendance stems from improved patient experience and a greater sense of partnership with the study team, supported by user-friendly, intuitive electronic patient-reported outcome (ePRO) tools.
2. Home-based visit compliance averaged 72% across Signant's patient engagement studies (including obesity, neurofibromatosis, and sickle cell disease) utilizing visit schedule modules and telehealth capabilities.

This also presents an opportunity to incorporate enhanced engagement features beyond visit information and telehealth, such as gamification, to further improve home-based completion compliance (Taylor et al., 2019).

These outcomes underscore a fundamental principle: **When patients feel supported, informed, and engaged through tools that reduce trial participation burden and support participant engagement and participant-centered reporting, they demonstrate good compliance rates.**



Goal setting is key in behavioral engagement and retention

While the evidence presented thus far demonstrates the effectiveness of self-monitoring and multicomponent interventions, recent systematic analysis reveals that the specific implementation of goal-setting strategies critically influences both behavioral engagement and retention outcomes. Understanding which goal-setting approaches produce optimal results enables more precise intervention design.

Systematic evidence on goal-setting implementation

A comprehensive review of 24 studies including 21 randomized controlled trials (2016-2025) with over 5,000 participants across diverse settings examined the effectiveness of goal-setting interventions specifically designed for weight, diet, or physical activity (Crooks et al., 2025, ECO poster presentation). This systematic analysis extracted implementation characteristics including goal-setting approach, support mechanisms, intervention intensity, and both behavioral and weight outcomes.

The findings reveal a nuanced picture: goal-setting interventions more consistently improved behavioral outcomes than weight outcomes, with clinically meaningful weight loss (≥5%) achieved in only a minority of studies. Importantly, several trials demonstrated behavioral improvements without corresponding weight changes compared to controls, suggesting that goal-setting's primary mechanism operates through behavior modification that may precede or occur independently of weight change.

Optimal goal-setting approaches

Analysis of implementation strategies revealed clear patterns in effectiveness:

Adaptive Goals

Adaptive, percentile-based goals consistently outperformed static targets. This approach adjusts goals based on individual progress and relative performance, creating achievable yet challenging targets that maintain motivation throughout the intervention period.

Dietary Goals

Dietary goals demonstrated substantially higher improvement rates (71%) compared with weight-loss goals (39%) based on change in Goal Attainment Scale (GAS) score. Goal categories included increasing fruit and vegetable intake, improving overall diet quality (fewer snacks, processed foods, sweetened beverages, and refined carbohydrates), targeting calories and salt, and increasing hydration while reducing days spent stressing about food decisions. This finding suggests that focusing on controllable behaviors (food choices, portion sizes, meal timing) rather than outcome measures (weight) produces stronger engagement and adherence.

Coping-planning

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, particularly for physical activity.

Engagement Frequency

High weekly engagement yielded the strongest effects on both weight and HbA1c. Regular, frequent interaction with goal-setting systems maintained participant attention and enabled timely adjustment of strategies when progress stalled.

Implementation parameters for trial design

Obesity trials should be designed to reflect current FDA expectations by using sustained weight loss over at least one year as a primary endpoint and favoring continuous weight measures to capture the full spectrum of response (FDA, 2025).

Engagement duration: Where between-group differences in retention were observed, goal-setting interventions noticeably enhanced engagement and moderately improved retention relative to non-goal-focused comparators. Structured weekly engagement should extend beyond six months to produce sustained behavioral change. In parallel, selection of fit-for-purpose clinical outcome assessments that capture symptoms, functioning, and daily life impacts most relevant to PLWO aligns with FDA 2025 guidance and reinforces participant engagement by measuring outcomes they care about.

Across the included goal-setting trials, retention to the primary endpoint among randomized participants was generally high (often around 80-90% or higher) where retention metrics were reported, substantially exceeding the typical retention rates in AOM trials. Behavioral goals consistently produced significant proximal outcomes (increased steps, reduced energy intake), where weight goals rarely translated to significant between-group weight differences, suggesting behavioral goals are the more reliably effective goal-setting intervention component, while weight goals alone are insufficient. This finding reinforces that structured behavioral engagement tools contribute meaningfully to participant retention.

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.

Integration with patient engagement strategies

These findings have direct implications for the comprehensive patient engagement strategies discussed throughout this paper. Goal setting should not be implemented in isolation but rather integrated into a broader ecosystem of support:

1. **Digital platforms** should enable adaptive goal adjustment based on individual progress data, moving beyond static target assignment toward personalized, percentile-based approaches.
2. **Educational resources** should emphasize dietary and physical activity goals rather than exclusively focusing on weight targets, helping participants understand that behavior change is the mechanism through which weight outcomes eventually occur.
3. **Coping-planning modules** should be systematically paired with goal-setting features, ensuring participants develop concrete strategies for overcoming anticipated barriers to goal achievement.
4. **Engagement touchpoints** should focus on data-driven goal review, progress feedback, and goal adjustment via frequent digital interactions (with daily self-monitoring and at least weekly goal cycles), supplemented by targeted early human support rather than relying on frequent, resource-intensive in-person visits.
5. **Predictive analytics** can identify participants whose behavioral goal achievement diverges from typical patterns, triggering targeted support interventions before behavioral disengagement progresses to study discontinuation.

The systematic evidence on goal-setting implementation reinforces a fundamental principle: the quality and specificity of behavioral engagement strategies matter enormously. Simply including "goal setting" in a trial protocol is insufficient; **the approach must be adaptive, behavior-focused, supported by coping-planning resources, and sustained through frequent engagement to achieve meaningful effects on both behavior and retention**.

Moving toward predictive, data-driven engagement

While the evidence-based strategies described above provide substantial benefits, the future of obesity trial retention lies in predictive approaches that identify at-risk patients before discontinuation occurs. This represents a fundamental shift from reactive to proactive patient support.

The rationale for predictive approaches

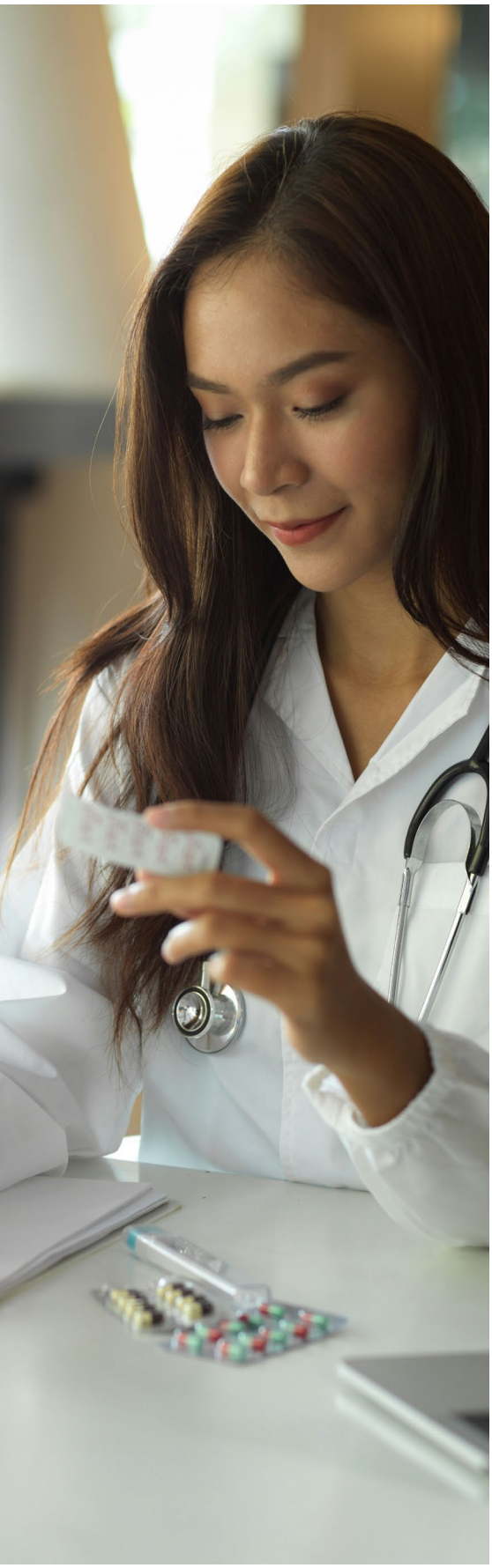
Traditional retention strategies apply uniform interventions across all participants, regardless of individual risk profiles. This approach fails to account for the heterogeneity in patient trajectories and the varying factors that drive discontinuation decisions for different individuals.

Predictive analytics enable targeted intervention by identifying behavioral patterns that precede dropout events. By analyzing ePRO metadata patterns (completion rates, timing trends, response delays) in combination with clinical data (weight loss trajectories, visit history, titration patterns), algorithms can generate real-time risk assessments and risk stratification that trigger targeted support interventions.

To avoid introducing data or algorithmic bias, these models should be trained and evaluated using standardized data streams and accompanied by consistent information and support offers to all participants, regardless of risk status.

Distinguishing efficacy perception from other risk factors

Emerging evidence suggests that advanced analytical approaches applied to longitudinal electronic clinical outcome assessment (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). This distinction is particularly critical in obesity trials, where perceived treatment efficacy is a key determinant of motivation to continue participation. By integrating early weight loss data with engagement metrics (frequency of log-ins, weight-ins, self-monitoring of diet and activity, completion of program content or ePROs, and responsiveness to study communications) (Johnson et al., 2026), site staff can define prespecified thresholds that trigger timely outreach to at-risk participants to proactively address concerns about treatment effectiveness, adjust support strategies for individual patients, and provide personalized encouragement based on objective evidence of clinical response.



Implementation considerations

Predictive engagement systems require careful implementation to ensure they enhance rather than burden site operations. Key considerations include:

- **Data integration architecture** that allows seamless flow of information from multiple sources (ePRO systems, electronic data capture (EDC) platforms, visit tracking systems) into unified analytical frameworks.
- **Real-time scoring and alerting** that generates risk indicator scores triggering targeted site interventions for high-risk patients.
- **Clear escalation protocols** that define specific actions for different risk profiles, ensuring that predictive insights translate into concrete support activities.
- **Ongoing performance monitoring** to assess the effectiveness of interventions and refine algorithms based on accumulating evidence from each trial, as well as monitor calibration and discrimination to assess fairness across subgroups (sex, age, race, socioeconomic status), as psychological predictors and engagement patterns can differ between groups.

Comprehensive prevention strategies: a systematic approach

Addressing patient attrition in AOM trials requires systematic intervention across multiple trial phases and stakeholder groups. Our experience suggests that effective prevention combines technological solutions with process improvements and behavioral interventions.

Education and training initiatives

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. Setting appropriate expectations about both the pace and magnitude of weight loss reduces the likelihood of discontinuation driven by mismatched expectations. These education efforts should also reflect regulatory priorities by explaining how obesity treatment interacts with comorbid conditions, including changes in antihypertensive and antidiabetic medications that regulators expect to see captured as secondary outcomes.

Site staff training to recognize and address obesity bias ensures that patients are respected and supported throughout trial participation. There is a well-documented stigma associated with obesity, therefore creating a supportive, non-judgmental environment is critical for retention.

Patient-centric digital solutions

Implementation of digital tools that reduce participant burden and enable remote participation can substantially improve retention. These solutions include:

Electronic data capture systems with intuitive interfaces that minimize the time and effort required for data entry while ensuring complete, high-quality data collection.

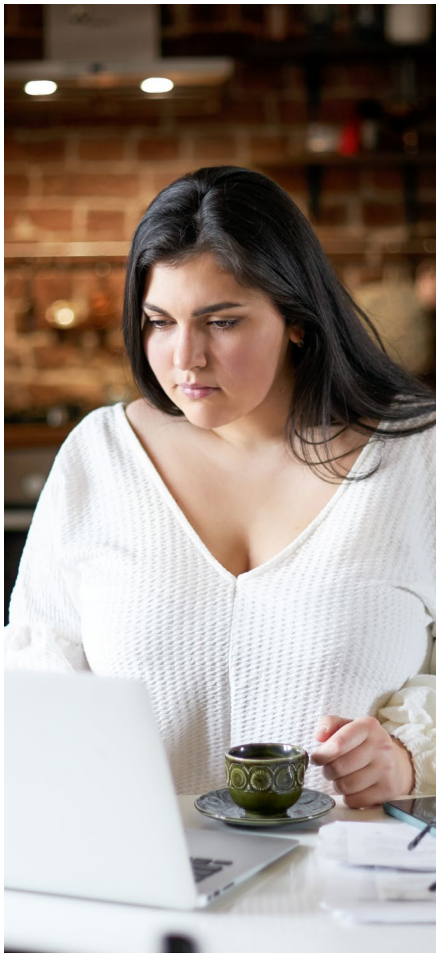
Telehealth capabilities that reduce the need for in-person visits, particularly for routine assessments that do not require physical examination.

Visit schedule modules that provide patients with clear information about upcoming requirements and send automated reminders to reduce missed appointments.

Real-time compliance monitoring that enables early identification of declining engagement and triggers proactive outreach.

Ongoing support programs

Structured support programs including dietitian consultations, regular check-ins, and self-monitoring tools help patients feel connected to their trial journey and provide practical assistance with the challenges of weight management. The evidence clearly demonstrates that regular contact with qualified professionals strengthens retention.



Clinical implications and the path forward

The convergence of systematic evidence, large-scale implementation experience, and advanced analytical capabilities creates unprecedented opportunities for improving retention in AOM trials. However, realizing this potential requires sustained commitment from all stakeholders in the clinical research enterprise.

Given that there is currently no evidence that PLWO will remain engaged for full trial duration or will be able to access AOMs following study completion, implementing robust patient engagement strategies is not optional. These approaches are critical for trial success and for ensuring that patients who volunteer for clinical research receive meaningful support throughout their participation.

Success demands recognition that attrition represents a system-level problem requiring system-level solutions. Individual sites, investigators, or sponsors cannot address this challenge in isolation. It requires coordinated effort across the entire clinical research ecosystem, with engagement strategies embedded systematically into trial design, execution, and monitoring.

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.

Moving from recognition to implementation

The clinical trial community has both an opportunity and a responsibility to proactively address early termination of treatment or study discontinuation through collaborative strategies. By implementing evidence-based engagement approaches, leveraging predictive analytics, and maintaining focus on patient-centered design principles, we can fundamentally improve retention rates while ensuring participants feel informed, supported, and valued throughout (and beyond) the trial experience.

As we continue to develop and refine AOMs with the potential to transform treatment for millions of PLWO, our success will depend not just on the pharmacological properties of these compounds, but on our ability to support the individuals who make clinical research possible through their participation.

Comorbidity assessment and special populations

Eligibility criteria typically enroll adults with BMI ≥30 kg/m², or ≥27 kg/m² with at least one weight-related comorbidity, consistent with current FDA 2025 obesity drug guidance, and require prospective collection of data on initiation, discontinuation, or dose reduction of medications for obesity-related conditions such as hypertension and Type 2 diabetes. These design features link retention directly to the ability to demonstrate durable effects on both weight and cardiometabolic risk.

The FDA 2025 guidance expands safety monitoring requirements to include comprehensive cardiovascular assessment, neuropsychiatric evaluation, immunogenicity testing, and abuse liability assessment. This expanded safety focus necessitates regular, sustained patient contact throughout the trial duration, making engagement strategies essential not only for efficacy measurement but also for adequate safety characterization. Addressing safety transparently can foster trust, necessary for the retention of patients.

Together, these regulatory expectations define the context in which patient engagement strategies must operate, making sustained retention a fundamental prerequisite for demonstrating long-term efficacy, comprehensive safety, and ultimately securing regulatory approval.

Mental health considerations in WMM trials

Previous experience has identified potential mental health implications associated with incretin-based AOMs and centrally-acting AOMs, making neuropsychiatric monitoring an essential component of obesity trial safety assessment (Arillotta et al., 2023). Research analyzing social media platforms revealed mental health concerns among patients using these medications, underscoring the importance of systematic monitoring. Reflecting these concerns, 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 Patient Health Questionnaire-9 (PHQ-9) and Columbia-Suicide Severity Rating Scale (C-SSRS) in obesity trials (FDA, 2025).

From a patient engagement perspective, these safety requirements create additional touchpoints with participants while also necessitating sensitive, stigma-free communication. 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 integration of mental health monitoring into broader engagement strategies ensures that patients feel supported across all dimensions of their trial experience.

Our path forward

Signant's path forward is to make patient retention, data quality, and equity the organizing principles of obesity trial design, not add-on features. Building on our experience across global incretin-based and other AOM programs, we have shifted from reactive problem-solving to a proactive, analytics-driven operating model that anticipates discontinuation risk and standardizes best practices at scale.

Our first priority is data quality monitoring that is continuous, centralized, and actionable. We integrate real-time monitoring across ePRO, EDC, and visit-tracking systems, with automated alerts for missing data, protocol deviations, and aberrant values, enabling early site intervention rather than remediation at database lock. Standardized data quality rules and cross-study lessons learned ensure that every trial benefits from the experience of the entire portfolio.

Second, we embed risk stratification and predictive analytics into routine trial operations. Using longitudinal engagement patterns, ePRO metadata, and early weight-loss trajectories, we identify participants at higher risk for dropout or non-adherence and trigger tiered support pathways ranging from automated digital reminders to targeted site outreach and tailored counseling. This same framework is used to flag sites with emerging performance issues, allowing us to direct training and resources where they have the greatest impact.

Third, patient retention is treated as a designed outcome, supported by standardized engagement packages that combine adaptive goal-setting, dietitian and site support, and flexible visit options (telehealth functionality). These interventions are templated, configurable, and consistently implemented across regions, reducing variability while allowing for appropriate local adaptation. Our goal is to make high patient retention the default expectation rather than an exceptional result.

Finally, we systematically reduce bias and enhance standardization in both measurement and delivery. This includes harmonized training and calibration for site staff, standardized digital workflows that minimize discretionary differences, and analytic checks for differential engagement or outcomes across demographic subgroups, with predefined actions to address any detected inequities. By unifying data quality monitoring, predictive risk stratification, and bias-aware standardization in a single operating framework, Signant provides sponsors with AOM trials that are more efficient, patient-centered, and aligned with evolving regulatory expectations.

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