Whitepaper:

OPTIMIZING CLINICAL TRIAL DESIGN AND STUDY EXECUTION IN OBESITY: A MEDPACE APPROACH

INTRODUCTION

Despite increasing awareness of the negative health outcomes associated with obesity, the prevalence of obesity continues to increase both in the US and globally.[1] Recent breakthroughs in the development and approval of novel anti-obesity drugs hold much promise and have reinvigorated this field. In this whitepaper, Medpace experts describe some of the key elements of study design and how these can be optimized to achieve successful study execution, with particular emphasis on managing rapid enrollment and maximizing patient retention in clinical trials.

STUDY DESIGN

Primary And Secondary Endpoint Selection

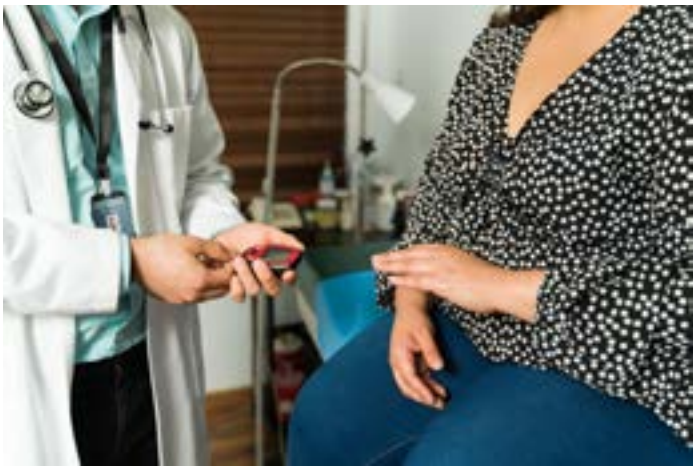
The FDA Guidance for Industry: Developing Products for Weight Management (Feb 2007) states that for phase 3 trials in obesity, the primary endpoint should include the difference in mean percent loss of baseline body weight in the active-product vs. placebo-treated group.[2] However, for a new anti-obesity drug to be successful, it must not only achieve a competitive amount of body weight loss (BWL) but should have additional effects to differentiate from existing marketed products (such as improvements in glycemic and metabolic parameters, improvements in QoL, or preferential loss of body fat mass). Some more recent trials such as the phase 2 trial of bimagrumab in obese/overweight patients with type 2 diabetes mellitus (T2DM) have utilized a Change From Baseline in total body fat mass by Dual-energy X-ray absorptiometry (DXA) as the primary endpoint.[3] The benchmark STEP clinical trials of semaglutide in obesity also included DXA sub-studies, which demonstrated changes in body composition including reduction in total fat mass and regional visceral fat mass as well as increased proportion of lean body mass relative to total body mass in STEP-1.[7]

DXA imaging can provide important body composition data for study endpoints and is easy to perform with minimal radiation exposure. DXA assessments can provide data to differentiate changes in central versus appendicular or sub-regional changes in fat distribution, as well as having the ability to assess both muscle and bone mineral density (BMD) to ensure weight loss is not driven by losses in these compartments. Operationally, DXA can utilize "reflection" imaging to image half of the body and extrapolate for full body image in subjects who may not fit the area of the scanner. Centralized reading of DXA allows for standardized placement of regions of interest (ROIs) to accurately track changes over time and across subjects and study centers. Medpace has extensive experience in running obesity trials with imaging such as DXA and MRI, and we would be happy to support your clinical trial needs.

STUDY TREATMENT DURATION

The optimal study treatment duration will depend on the stage of clinical development of your anti-obesity agent. For Sponsors who approach Medpace with compounds at Early Clinical Development, for example, for the First-In-Human (FIH) trial - we would recommend a combined Single and Multiple Ascending Dose (MAD) study, which can be conducted in an overweight/obese, but otherwise healthy adult population. The dosing duration for the MAD can be utilized to obtain preliminary efficacy data on BWL, for example after 4-6 weeks. An exploratory meta-analysis of early (week 4) and longer-term (3-6 months) weight loss with various anti-obesity agents has shown a strong relationship between treatment-related early and longer-term weight loss, which appears to be independent of mechanism of action.[15] Medpace has a dedicated Clinical Pharmacology Unit (CPU) located at our Cincinnati campus, which is experienced in running FIH anti-obesity trials, and we currently have a database of approximately 7,000 healthy overweight or obese subjects.

Medpace has robust experience conducting phase 2-3 trials for a wide range of anti-obesity agents, including centrally acting agents, GLP-1 agonists, GLP-GIP co-agonists, and combination therapy anti-obesity products, both in general obesity populations as well as specialized obesity populations (e.g. Prader-Willi Syndrome). We have conducted smaller phase 2 studies with hundreds of subjects, to very large phase 3 obesity programs with several thousand subjects. The treatment duration for these later phase studies are typically 6 months-12 months, with the FDA Guidance for Industry: Developing Products for Weight Management recommending approximately 3,000 subjects in total for the anti-obesity program randomized to active doses of the study drug, and no fewer than 1,500 subjects randomized to placebo for 1 year of treatment.[2]



INTEGRATING WITH STANDARD OF CARE

As with any disease with an established treatment paradigm, the current standard of care for obesity must be taken into consideration when designing clinical trials. Current standard of care includes dietary recommendations, physical activity recommendations, approved obesity medications, bariatric surgery, as well as behavioral and psychologic counseling. Typically, the core pillars of lifestyle intervention are included in trial protocols, with a recommendation for 500 kcal per day deficient and 150 minutes of exercise per week, while more comprehensive lifestyle programs or commercial weight loss programs are not included or prohibited to avoid confounding weight loss efficacy data.

While encouraging and supporting healthy lifestyle choices for both diet and physical activity is a standard study design element, other non-pharmacological treatment options are routinely prohibited due to possible confounding of study data. These include recent bariatric surgery, weight management programs focused on the psychological aspects of this condition (e.g., cognitive-behavioral therapy for correcting eating disorders), and intensive programs driven by the booming fitness industry.

In regard to approved medications, several classes of anti-obesity agents are available to patients in addition to lifestyle modification. Currently approved medications for weight loss include orlistat (Xenical, Alli), phentermine/topiramate extended-release (Qsymia), naltrexone/bupropion ER (Contrave), liraglutide (Saxenda), semaglutide (Wegovy), and setmelanotide (Imcivree).[4] While these medications are prohibited in most clinical trials, prior use should not be exclusionary as long as body weight has been stable for an appropriate duration prior to screening or randomization.

While newly implemented interventions for weight management that could confound study endpoints must be avoided for study data integrity, finding a way to balance the needs of the patient and the needs of the study will result in better outcomes for both.

STUDY EXECUTION

Managing Rapid Enrollment

Unlike many trials in chronic diseases, obesity trials tend to have great enthusiasm from potential subjects who are motivated to participate by the hope for rapid and easy weight loss. Of note, enrollment is often skewed to more female than male subjects. Given that screening and enrollment rates can be higher than in most other metabolic indications, 6 patients/site/month (p/s/m) and 2.9 p/s/m respectively, Medpace works with study sites to plan proactively to manage the high volume of subject visits, laboratory data, diary data, and ensure timely entry of data into EDC. We work with our sponsors to be prepared to have prompt monitoring visits and identify any errors in study conduct quickly, so that retraining can occur and data integrity can be maintained.

Data monitoring and reviews for both data quality and safety need to be set up to begin during the first weeks of enrollment, as there is unlikely to be a lag between first patient in (FPI) and 10-25% of subjects enrolled. Review of data by medical, clinical operations, and data management teams must occur more frequently than

in slower recruiting studies to avoid a large backlog of data pending review and to address any data collection or data integrity concerns in a timely manner. Other practical considerations include having enough central laboratory kits, adequate study drug supply, and other study supplies on site and rapid methods for triggering and completing re-supply functions.

While competitive enrollment is usually recommended, guaranteeing all sites a minimum period of time (ie, 1-2 months) during which they can enroll a pre-specified number of subjects helps to motivate sites to complete all steps for site activation promptly while also ensuring that the entire study is not primarily enrolled by the few fastest sites. Regular teleconferences with Investigators and site staff can also aid in managing expectations and keeping sites informed as to study status and pace of recruitment. We find that these teleconferences are well attended and often result in better dissemination of information than email newsletters which may not be reviewed as thoroughly by investigators.

MINIMIZING PATIENT DROP OUT AND MAXIMIZING PATIENT RETENTION

Our own Medpace experience indicates that the growing competition in the anti-obesity arena may contribute significantly to an increase in early discontinuation rates for subjects in phase 2-3 clinical trials in this indication. Historically, dropout rates in obesity studies of one-year duration have been as high as 50%. For example, in the Contrave (naltrexone/bupropion [NB]) phase 3 program of 5 studies with 1,515 placebo treated and 3,239 Contrave treated subjects, the average discontinuation rate was over 45% across treatment groups with the highest discontinuation rate of over 60% in the highest dose Contrave group.[6]

This well-known challenge of high subject discontinuation rates in the clinical development of anti-obesity agents is primarily attributed to three key reasons: (1) perceived effect (or its absence) regarding weight loss, (2) tolerability of study drug and study requirements, and (3) access to alternative treatment options. The balance between these three variables plays a crucial role in individual decisions to either continue participating in any clinical trial or withdraw consent and end study participation.

Perceived Effect or its Absence

While there is an altruistic component to study participation, subjects are often more likely to remain committed to a study when there is the possibility of some personal benefit, and our experience is that the potential for weight loss is a key driver for obese patients to join and remain in clinical trials. In an analysis of the rates and reasons for early discontinuation in our recent obesity studies, over 80% of subjects who withdrew consent or were lost-to-follow-up had weight gain or minimal weight loss (<5%) at their final study visit. These discontinuations which may be driven by a perceived lack of efficacy often occur early in study participation, i.e. during first 3 months of a one-year study, not just when subjects have been enrolled for greater than 6 months with no perceived personal benefit.

Many study subjects measure the effect of the study drug in terms of kilograms of weight loss, and they may tend to underestimate other positive health effects and devalue small weight loss that can be achieved by complying with the diet and physical activity recommendations provided as part of the clinical trial. Based on our experience, we have observed that investigators who are experts in this field are adept at addressing such issues with subjects from the outset. Discussing expectations with their subjects prior to study randomization allows these investigators to set subject expectations and ensure selection of subjects with an eye toward retention. If a subject is showing signs of not being fully committed to study participation despite potential effects observed, it is likely this subject would not be a good candidate to move forward in study participation. Furthermore, investigational sites may have their unique programs that encompass step-by-step planning of long-term weight loss, establishing realistic expectations, and adjusting them based on interim results, as well as providing education on health benefits that extend beyond measurable weight loss. With respect to a personalized approach to treating people with obesity, our goal is to strike a balance between site-specific weight management programs and the clinical trial protocol, leveraging the best practices from real medical settings while safeguarding clinical data against any potential bias and ensuring essential standardization of clinical trial procedures.

Our database of experienced investigators in this field enables us to conduct clinical trials within our network. However, if there is a need to include new investigational sites, our feasibility assessment process will include exploring site-specific approaches to treating patients with obesity. This includes evaluating diet and physical activity recommendations, the use of diaries, mobile applications, and other educational tools, as well as potential collaborations with fitness and healthcare organizations.

We have developed our own tools to facilitate discussions about subjects' expectations of results, including tips on how to address the most common concerns. We have found it very helpful to educate subjects on the mechanism of action of the investigational product beyond weight loss effect. Our Patient Recruitment and Retention (PRR) team has experience in developing materials using people-first language to explain complex topics such as the mechanism of action in graphic or other easy-to-comprehend formats. Effects such as increased muscle mass, improved lipid and glucose profiles, and cardio-renal protective effects, which can be achieved by adhering to diet and physical activity recommendations, should be consistently emphasized to subjects throughout their participation in the clinical trial.

For placebo-controlled studies, the addition of an open-label extension (OLE) period with all subjects receiving an active study drug may also motivate subjects to continue study participation even if significant weight loss does not occur, as there is the possibility of further benefit during the OLE period. Medpace has significant experience conducting studies with an OLE component as well as programs with OLE studies in rare disease and metabolic indications. While most OLE are performed primarily for the purpose of obtaining long-term safety and efficacy data, Investigator feedback has been that subjects are more willing to enroll in a placebo-controlled study with an OLE component as subjects know they will have the opportunity to receive active study drug during OLE participation. In addition to the positive impact on subject retention, an OLE period with active treatment allows for the collection of additional efficacy and safety data.

Tolerability

Before we delve into the tolerability of investigational treatments, which is a product-specific topic, we would like to discuss the tolerability of the diet and lifestyle interventions that are required or recommended as per the protocol, as well as the overall burden of study procedures on subjects.

The most common and fundamental diet and physical activity intervention includes a 500 calorie deficit per day and 150 minutes of physical activity per week. This approach was used in the STEP-1 study.[7] Participants received individual counseling sessions every 4 weeks to help them adhere to a reduced-calorie diet (500-kcal deficit per day relative to the energy expenditure estimated at the time of randomization) and increased physical activity (150 minutes per week of physical activity, such as walking, encouraged).

However, in the STEP-3 study, intensive behavioral therapy was required as a background treatment.[8] For the first 8 weeks after randomization, participants received a low-calorie diet (1000-1200 kcal/d) provided as meal replacements (eg, liquid shakes, meal bars, portion-controlled meals [provided by Nutrisystem, supplied by the Sponsor]). Participants subsequently transitioned to a hypocaloric diet (1200-1800 kcal/d) of conventional food for the remainder of the 68 weeks, with prescribed calorie intake based on randomization body weight. At randomization, participants were prescribed 100 minutes of physical activity per week (spread across 4-5 days), which increased by 25 minutes every 4 weeks, to reach 200 minutes per week. During the 68 weeks, participants were provided with 30 individual intensive behavioral therapy visits with a registered dietitian, who instructed them in diet, physical activity, and behavioral strategies.

Drop-out rates in STEP-1 and STEP-3 studies were 5.7% (5% active arm, 7% placebo) and 17.3% (16.7% active arm, 18.6% placebo), respectively. Although several factors may explain the significant difference in drop-out rates between the STEP-1 and STEP-3 studies, the tolerability of the protocol-specific diet might have been one of them, considering that diet fatigue is a well-known phenomenon. Despite initial enthusiasm, subjects may not be able to maintain a more intensive lifestyle intervention, particularly when they encounter weight plateaus and find that their efforts in maintaining a hypocaloric diet do not

correspond to the expected weight loss effect. When a more restrictive diet is required per protocol, a higher rate of withdrawal of consent by subjects can be anticipated.

As for product-specific tolerability issues, there are well-known gastrointestinal (GI) adverse events observed in clinical trials of GLP-1 and other incretin-based products. To improve tolerability, a gradual study drug dose titration approach may be useful, as defined by the unique PK/PD characteristics of each investigational product. If GI symptoms are likely based on the mechanism of action, slow up-titration of study drug dose should be performed over several weeks or visits to improve tolerability. If severe or intolerable GI symptoms do occur, it is helpful to allow down-titration of dose and/or temporary discontinuation of the study drug to retain subjects in the study. Retention may also be improved by allowing subjects to continue participating in the study on lower doses of study drug if higher doses are poorly tolerated. The study analysis plan should address how data will be analyzed for subjects who are unable to achieve the target doses planned for the study. When resuming study treatment after a prolonged interruption, it is often prudent to start with the lower dose and re-titrate (if blinding scheme and drug supply allows) to avoid tolerability concerns with an abrupt re-initiation of full dose. Another option to manage GI or other anticipated side effects is to include protocol guidance on the use of pharmaceutical agents to treat specific symptoms, per local guidelines.

Access to Alternative Treatment Options

As discussed above, the primary driver for a person with obesity to take part in a clinical trial is their motivation to achieve weight loss. If weight loss does not occur or occurs at a slower pace than desired, the subject may consider alternative methods to achieving weight loss. If those other options are readily available without significant cost (either financial or effort), then this subject has a higher likelihood of pursuing those other treatment options and dropping out of the clinical trial. In this case, prompt recognition of this risk and addressing it by reminding the subject of the positive aspects of trial participation in conjunction with a strong relationship with the Investigator or other site staff are critical to successful retention and completion of study assessments.

In addition to approved obesity medications, patients may seek alternative treatment with products of the same class as approved weight loss medications and marketed for diabetes but used off-label for obesity, as well as other ongoing and planned clinical trials of novel anti-obesity investigational products and new formulations of approved products, particularly the oral formulation of semaglutide.[5] Of note, in the OASIS-4 study of oral semaglutide 25 mg (NCT05564117), the enrollment rate was 4.27 p/s/m, which was higher than the average enrollment rate observed in this indication, suggesting enthusiasm for continued optimization of drugs with well-established efficacy.[16] Several approved anti-obesity drugs remain under active clinical development, which adds to the alternative therapeutic options available to subjects, although recent use of another investigational product may limit clinical trial participation.

Given this competitive landscape, we must consider ways to design trials that subjects are motivated and able to successfully complete. In trials of T2DM, a well-established study design element for both retention and subject safety is glycemic rescue therapy, such that a subject with fasting plasma glucose and/or HbA1c above pre-set thresholds at certain timepoints in study participation will be offered additional standard-of-care therapies to improve diabetes management.[9] If we translate rescue therapy to an obesity study, subjects with no weight loss (or weight loss <2%, for example) at pre-specified time points (e.g., Week 12, Week 24, etc.) could be offered more intensive dietary or behavioral counseling, and if continued lack of weight loss at next milestone visit, then active

treatment with an approved medication could be offered as "rescue". If a standard-of-care medication could be offered which is potentially complementary to the investigational product, then the subject could remain on a blinded study drug, adding to the safety dataset and possibly generating preliminary data on combination therapy. Several instances of rescue therapy did occur in both the semaglutide STEP-1 and STEP-4 studies. In STEP-1, rescue interventions were received by 7 participants in the semaglutide group (2 had bariatric surgery and 5 received other anti-obesity medication) and by 13 in the placebo group (3 had bariatric surgery and 10 received other anti-obesity medication).[7] In STEP-4, one participant on placebo received rescue intervention (liraglutide) during the randomized period.[17]

While current phase 2-3 obesity studies are designed to compare study drug to placebo, we may eventually transition to non-inferiority studies for obesity with an active comparator as recently approved therapies become the routine standard of care. A precedent of such a transition in study design is well known for clinical trials in T2DM. Retention in clinical trials with an approved anti-obesity comparator won't be as challenging as in placebo-controlled studies, and even more rapid enrollment can be anticipated. As an example, we can refer to the phase 2 clinical trial of cagrilintide for weight management in people with overweight and obesity (NCT03856047).[10] In this 12-armed study with 5 doses of cagrilintide compared to liraglutide and volume-matched placebo, only 101 subjects out of 706 randomized subjects receiving placebo. This low chance of receiving placebo may have played a role in subject retention, with only 4% of subjects across treatment groups withdrawing consent. In addition, the enrollment rate in the cagrilintide study was 2.[2] p/s/m, however even higher enrollment rate of 3.[3] p/s/m was seen in a phase 2 study of bimagrumab with even lower chance of receiving only placebo.[11] That study had factorial assignment across 9 treatment arms to bimagrumab (0, 10, 30 mg/kg) or semaglutide (0, 1.0, or 2.4 mg) such that only 1 out of 9 subjects received no active treatment during the core treatment period and all subjects received active treatment in the 24-week extension period.

As patients have growing access to alternative therapies, they will be less accepting of placebo-controlled trials or at least seek to minimize their chance of receiving only placebo, as seen in the above examples. An ongoing Phase 3b study comparing the efficacy and safety of tirzepatide versus semaglutide in adults who have obesity or overweight will provide further insights into the impact of a comparative study design with active comparator on recruitment and retention rates.[14] Given the evolving landscape of weight loss therapies and interventions, the challenge lies in finding opportunities for complementary approaches in this complex arena while avoiding direct competition.

ENDNOTES

In this whitepaper, we have reviewed some of the key elements of obesity clinical trial design and how these can be optimized to achieve successful study execution, with particular emphasis on managing rapid enrollment and maximizing patient retention in these trials. While obesity remains a growing public health concern in the US and globally, the successful approval of many new products in recent years shows that many patients, healthcare providers, and regulators are motivated to find better options to manage this chronic metabolic disease.

Contact our expert team to learn how we can help.

REFERENCES

1. Centers for Disease Control and Prevention. (17 May 2022). Adult Obesity Facts. https://www.cdc.gov/obesity/data/adult.html
2. FDA. (February 2007). Guidance for Industry Developing Products for Weight Management. https://www.fda.gov/media/71252/download
3. Safety, Pharmacokinetics and Efficacy of Bimagrumab in Overweight and Obese Patients With Type 2 Diabetes. https://clinicaltrials.gov/ct2/show/NCT03005288
4. NIH. (n.d.) Prescription Medications to Treat Overweight & Obesity. https://www.niddk.nih.gov/health-information/weight-management/prescription-medications-treat-overweight-obesity
5. Novo Nordisk. (22 May 2023). Novo Nordisk A/S: Oral semaglutide 50 mg achieved 15.1% weight loss (17.4% if all people adhered to treatment) in adults with obesity or overweight in the OASIS 1 trial. https://www.novonordisk.com/news-and-media/news-and-ir-materials/news-details.html?id=166110
6. FDA. (2014). Center For Drug Evaluation And Research, Application Number: 200063orig1s000, Medical Review(s), Naltrexone HCl/Bupropion HCl (Contrave), Table 36. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/200063Orig1s000MedR.pdf
7. Wilding JP, Batterham RL, Calanna S, et al. (18 March 2021). Once-Weekly Semaglutide in Adults with Overweight or Obesity. N Engl J Med 2021; 384:989-1002. https://www.nejm.org/doi/full/10.1056/NEJMoa2032183
8. Wadden TA, Bailey TS, Billings LK, et al. Effect of Subcutaneous Semaglutide vs Placebo as an Adjunct to Intensive Behavioral Therapy on Body Weight in Adults With Overweight or Obesity: The STEP 3 Randomized Clinical Trial. JAMA. 2021;325(14):1403–1413. doi:10.1001/jama.2021.1831
9. FDA. (February 2008). Guidance for Industry Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention. https://www.regulations.gov/document/FDA-2008-D-0118-0003
10. Lau DCW, Erichsen L, Francisco AM, Satylganova A, le Roux CW, McGowan B, et al; Lancet VOLUME 398, ISSUE 10317, P2160-2172. (11 December 2021). Once-weekly cagrilintide for weight management in people with overweight and obesity: a multicentre, randomised, double-blind, placebo-controlled and active-controlled, dose-finding phase 2 trial; Nov 16, 2021. https://doi.org/10.1016/S0140-6736(21)01751-7
11. Safety and Efficacy of Bimagrumab and Semaglutide in Adults Who Are Overweight or Obese. https://clinicaltrials.gov/ct2/show/NCT05616013
12. Research Study to Investigate How Well Semaglutide Works Compared to Liraglutide in People Living With Overweight or Obesity (STEP 8). https://clinicaltrials.gov/ct2/show/results/NCT04074161
13. Jastreboff AM, Aronne LJ, Ahmad NN, et al. (21 July 2022). Tirzepatide Once Weekly for the Treatment of Obesity. N Engl J Med 2022; 387:205-216. https://www.nejm.org/doi/full/10.1056/NEJMoa2206038
14. A Study of Tirzepatide (LY3298176) in Participants With Obesity or Overweight With Weight Related Comorbidities (SURMOUNT-5). https://clinicaltrials.gov/ct2/show/NCT05822830
15. Plock N, Bax L, Lee D, DeManno D, et al. (09 June 2016). Exploratory Literature Meta-Analysis to Characterize the Relationship Between Early and Longer Term Body Weight Loss for Antiobesity Compounds. The Journal of Clinical Pharmacology. https://pubmed.ncbi.nlm.nih.gov/27277818/
16. Research Study Looking at How Well Semaglutide Tablets Taken Once Daily Work in People Who Have a Body Weight Above the Healthy Range (OASIS 4) https://clinicaltrials.gov/ct2/show/NCT05564117?term=NCT05564117
17. Rubino D, Abrahamsson N, Davies M, et al. Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults With Overweight or Obesity: The STEP 4 Randomized Clinical Trial. JAMA. 2021;325(14):1414–1425. doi:10.1001/jama.2021.3224 https://jamanetwork.com/journals/jama/fullarticle/2777886