Advancing Research and Development of Multi-indication and Combination Therapies for Obesity

Obesity is commonly defined as excess fat accumulation that puts someone at a higher risk for adverse health outcomes.[1] The simplicity of this definition can be misleading, because obesity's pathophysiology is highly complex, and characterised by a multitude of interrelated factors, including metabolic and immune changes in response to energy surfeit; mechanisms such as oxidative stress, and local and systemic inflammatory responses; alterations in blood flow and perfusion; and the mechanical burden of weight. Together, these factors contribute to the morbidity and mortality of the many obesity-related conditions.

The interdependent pathophysiology of obesity and comorbid conditions are relevant to treatment efficacy and have informed an interdisciplinary approach to obesity treatment in recent years, including the development of single treatments for multiple indications and combination interventions. Indeed, in a 2023 ICON survey of more than 100 professionals engaged in obesity-related clinical research, only 37% reported studying obesity alone. The indications most commonly included in obesity-related research were reported to be diabetes (55%), metabolic disease (48%), mental health (39%) and cardiovascular disease (38%).

Multi-indication Trials

Historically, drug development proceeded one indication at a time, from diabetes to weight loss and MASH indications. But, encouraged by the recent approval of GLP-1 receptor agonists for obesity – in addition to type 2 diabetes, and an improved understanding of the shared pathophysiology of obesity and other comorbid conditions – that has begun to shift. In the ICON survey, 50% of respondents reported employing multi-indication studies in their obesity-related trials.

Innovative approaches to trial design are often needed to demonstrate a treatment's efficacy for multiple indications. Here, sponsors may benefit from the use of master protocols, which are constructed to include multiple sub-studies, which have an overarching set of procedures to improve efficiency, such as inclusion of a common screening protocol or the sharing of control subjects. Master protocols with a basket trial design are well suited for multi-indication treatments across the obesity related spectrum of diseases or for subtypes of a single disease, which have a common molecular characteristic.[2]

The Need for Long-term Follow-up

In the ICON survey, 44% of respondents reported that long-term follow-up was the biggest challenge in obesity-related clinical trials, Longer-term studies are needed to determine treatment effects on clinical events linked to obesity-related comorbidities, including major adverse cardiovascular events (MACE), chronic kidney disease and the onset of diabetes. This information is crucial for assessing the cost effectiveness of new treatments and will be required to compete with products that have proven outcome benefits.

Novo Nordisk's SELECT trial provides an excellent example. The primary endpoint of SELECT – a double-blind, parallel-group study evaluating weekly injections of the GLP-1 receptor agonist Wegovy® (semaglutide) in non-diabetic patients with a history of cardiovascular disease – was the reduction of MACE. In August 2023, Novo Nordisk reported a 20% reduction in MACE compared to placebo, outpacing the reduction analysts had been expecting, and boosting Wegovy's prospects clinically and financially.[3]

Long term outcomes trials are very costly and there is an imperative for creating efficiencies in their execution. High levels of retention and compliance contribute to efficiency. This can be driven by easing patient burden with decentralised and hybrid approaches to follow-up as ICON successfully demonstrated in a recent heart failure registrational trial.[4] Furthermore, we have employed our tokenisation capabilities to protect against loss of endpoint data and also to allow for continued data collection after the trial completes. Of note in the ICON survey only 22% of respondents were following patients beyond five years in their obesity-related clinical studies.

Traditional time-to-first-event analysis may lack efficiency compared with alternative approaches that have the potential to reduce sample size.[5] Many cardiovascular outcomes trials have been underpowered for confirmatory endpoints. The use of historic electronic medical record (EMR) data can be leveraged to inform sample size estimates to assure that studies are adequately powered including for the key secondary endpoints.

Combination Approaches to Obesity Treatment

New obesity therapies have to be developed in the context of adequate background lifestyle counselling.[6] As an example of this in practice, ICON is incorporating digital platforms to assure consistent counselling across study sites. The value of enhanced behavioural therapies was reflected by survey respondents, the majority of whom felt that this was a promising pathway for future treatment. Evolving digital therapeutic devices have the potential to advance the efficacy of long-term lifestyle interventions.

Even with recent advancements in obesity therapies only 17% of survey respondents felt that single pharmaceutical targets – such as GLP-1 receptor agonists – would dominate future research efforts. Instead, most respondents (64%) felt that there would likely be a focus on combination treatments.

Drug combinations have the potential to optimise a more personalized treatment approach. For example, GLP-1 receptor agonists result in loss of both fat and lean mass. Loss of lean mass is a particular concern for older patients with sarcopenia.[7] Here the addition of medications that preserve muscle mass may not only

improve the quality of weight loss but also enhance fat loss given the role of skeletal muscle in energy expenditure. Medications targeting new molecular pathways will provide additional opportunities to explore multidrug synergies.

Development Considerations for Combination Interventions

Sponsors wishing to develop combination therapies for obesity will face added complexity during treatment development. For one thing, they need to consider potential drug-drug interactions. As with multi-indication treatments, sponsors looking to validate combination treatments will need to employ innovative clinical trial designs. Here, master protocols using a platform trial design – which can evaluate and compare multiple interventions for one indication through multiple trial arms – may prove invaluable. Platform trials are adaptable, allowing researchers to begin additional arms or evaluate the results of an arm while the trial is ongoing. Moreover, a platform trial allows a greater percentage of participants to receive treatment, since only one of several arms receives a placebo.

Obesity Treatments Continue to Evolve

In recent decades, obesity has become a global epidemic, and there is a growing need for more effective treatments of this condition. Already, an increased understanding of obesity's complex pathophysiology has led to better treatments. However, continued efforts are needed, particularly in approaches to treatments that account for obesity as a multi-condition risk factor. These must be supported by strategic and innovative approaches to therapeutic development and clinical trials design.

REFERENCES

1. Purnell, Jonathan Q. "Definitions, Classification, and Epidemiology of Obesity." Endotext, edited by Kenneth R. Feingold et al., MDText.com, Inc., 2000, http://www.ncbi.nlm.nih.gov/books/NBK279167/.
2. Rhythm Pharmaceuticals. "Rhythm Pharmaceuticals Presents New Data from Phase 2 Basket Study Showing Continued Weight Loss at Up to Nine Months in Patients with HET Obesity on Setmelanotide at ENDO 2021." Press Release. March 2021. https://ir.rhythmtx.com/news-releases/news-release-details/rhythm-pharmaceuticals-presents-new-data-phase-2-basket-study
3. "SELECT: Semaglutide Reduces Risk of MACE in Adults With Overweight or Obesity." American College of Cardiology, https://www.acc.org/Latest-in-Cardiology/Articles/2023/08/10/14/29/http%3a%2f%2fwww.acc.org%2fLatest-in-Cardiology%2fArticles%2f2023%2f08%2f10%2f14%2f29%2fSELECT-Semaglutide-Reduces-Risk-of-MACE-in-Adults-With-Overweight-or-Obesity. Accessed 22 Sept. 2023
4. Claggett BL. Et al. Quantifying Treatment Effects in Trials with Multiple Event-Time Outcomes. NEJM Evid 2022; 1 (10) https://evidence.nejm.org/doi/full/10.1056/EVIDoa2200047
5. Spertus JA, et al. The SGLT2 inhibitor canagliflozin in heart failure: the CHIEF-HF remote, patient-centered randomized trial. Nat Med 2022 Apr;28(4):809-813. doi: 10.1038/s41591-022-01703-8. Epub 2022 Feb 28
6. Hall, Kevin D., and Scott Kahan. "Maintenance of Lost Weight and Long-Term Management of Obesity." The Medical Clinics of North America, vol. 102, no. 1, Jan. 2018, pp. 183–97, https://doi.org/10.1016/j.mcna.2017.08.012.
7. Ji T, Li Y, Ma L. Sarcopenic Obesity: An Emerging Public Health Problem. Aging Dis. 2022;13(2):379-388. Published 2022 Apr 1. doi:10.14336/AD.2021.1006

Dr. Jack L. Martin

Dr. Martin, MD, FACC, is board certified in Cardiovascular Diseases and Interventional Cardiology. He has over 35 years of clinical practice and investigational experience. Jack is an experienced consultant for pharmaceutical and medical device companies. This includes all phases of product development including device design, trial design, FDA pre-sub and panel meetings. Dr. Martin has served as study chairman or the coordinating investigator for multiple multicenter international pharmaceutical and device trials. His previous roles included Assistant Professor of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Chief, Division of Cardiovascular Diseases and Chief of Interventional Cardiology, Health System. He has served as President and a Board Member of several research foundations and is a respected educator having served as an Interventional Cardiology Fellowship Program Director. He has numerous peer-reviewed publications, is an active journal reviewer and has been a frequent invited speaker at national and international professional conferences. While at ICON, Jack has provided medical oversight for numerous cardiometabolic studies and has focused on cross functional team building to provide novel solutions for the effective delivery of drug and device trials.