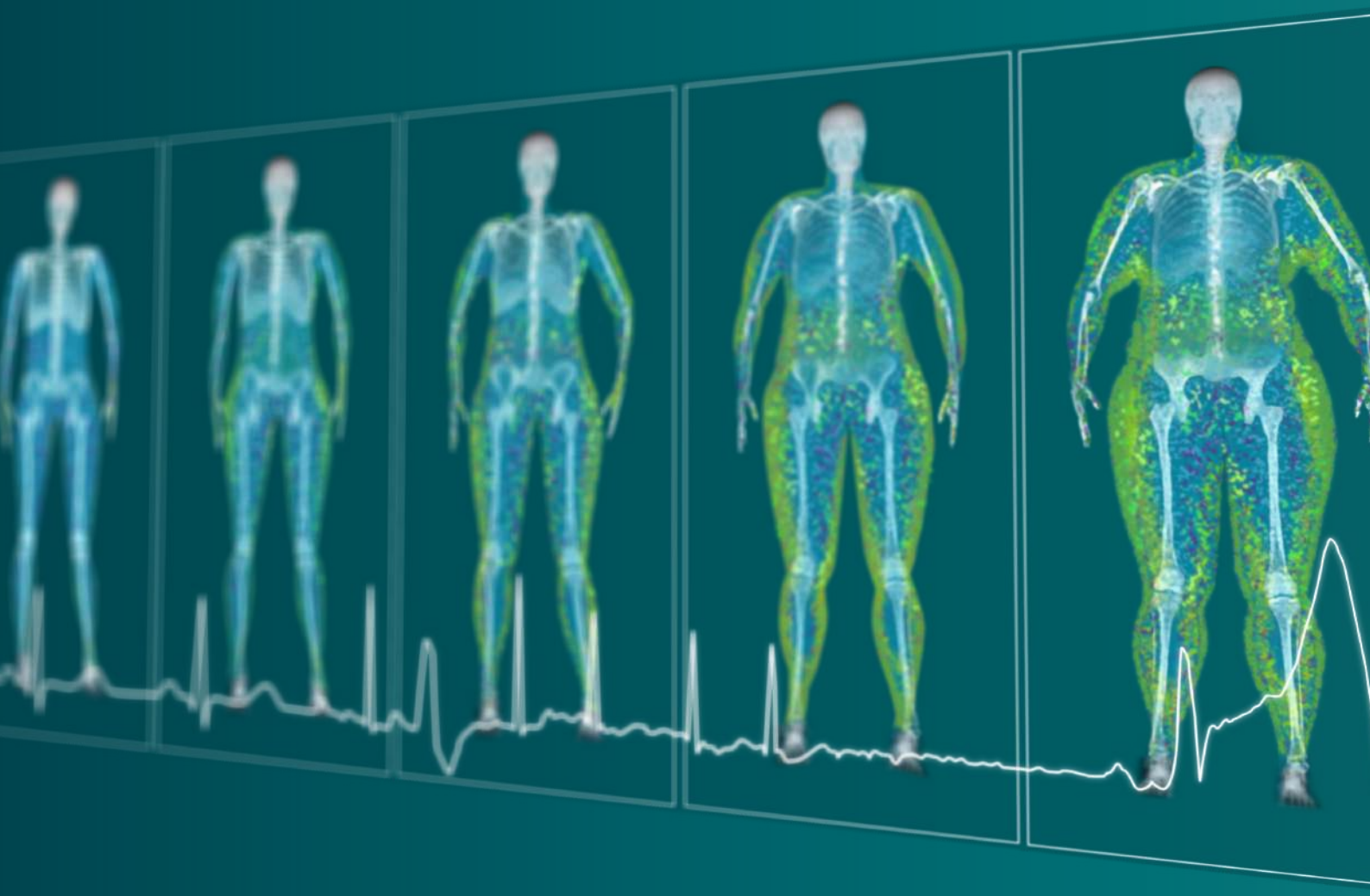
Whitepaper

A multifaceted risk factor:

Addressing obesity's impact across the disease spectrum



ICONplc.com/obesity

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Executive summary

Obesity is a growing health concern worldwide, with at least 2.8 million people dying each year as a result of the disease. As well, the number of individuals living with obesity continues to increase annually across age, gender and geographic location. A complex condition, obesity has implications in inflammatory, metabolic and cardiovascular health — which, together, mean that advancing the treatment of obesity also means taking into account its relationships with other physiological systems and health conditions.

Recently, treatment for obesity has made great strides, with newly approved drugs gaining a great deal of attention from patients, clinicians and providers alike. As sponsors and researchers look to progress the field of obesity treatment, there are a number of unique considerations to account for in their approach to development and clinical trials.

This whitepaper explores the implications of obesity as a risk factor across the disease spectrum, and how this may impact treatment, drug development and clinical trials for obesity. Readers can expect to learn:

– The foundational physiology and drivers of obesity

– How obesity impacts inflammatory, metabolic and cardiovascular health

– Current approaches to treating obesity

– Considerations for future obesity drug development, including long-term health solutions and multidisciplinary and combination therapies

– Unique challenges and approaches in participant recruitment and retention for obesity-related clinical trials

– Considerations for clinical trial design focused on obesity treatments

– Why and how to plan for long-term follow-up for obesity treatments

About the ICON obesity survey

ICON survey report: Trends and challenges in obesity research and clinical trials

As obesity rates continue to climb, research in obesity-related treatments, from drugs to devices, continues to make significant advances. Recent developments, including the approval of GLP-1 receptor agonists, such as semaglutide, to treat obesity, have sparked excitement in the field, and shined a light on the potential future of obesity treatment.

To better understand the current state of obesity-related treatment development, ICON conducted a survey of professionals engaged in obesity-related clinical research, representing organisations ranging from small biotechs to large pharmaceutical companies, as well as academic organisations. This survey investigates the opinions, experiences and predictions of a variety of individuals well positioned to provide an overview of current obesity drug and device development and where it is likely to go in the future.

Explore the results to learn:

– The most promising interventional pathways for obesity, present and future

– The areas and indications included in current obesity research

– The biggest challenges in obesity-related development and clinical trials

– Factors impacting clinical trial recruitment and retention, including improving diversity of patient populations

– Predictions of the future of obesity research, from pipeline success to therapeutic focus

Select findings from this survey will be featured in the following whitepaper. For more information, and to view the complete results, download the full survey.

ICONplc.com/obesity-survey-report

Introduction

Over the last several decades, obesity has become a global epidemic of public health urgency. The World Obesity Federation estimates that by 2030, more than one billion of the world's population, or roughly one in five women and one in seven men, will be living with obesity.[1]

However, the problem – which has reached epidemic proportions worldwide, with at least 2.8 million people dying each year as a result of the disease – is not just limited to adults.[2] Children are also becoming increasingly impacted, with global obesity rates for this group increasing from 4% in 1975 to more than 18% in 2016.[3] Additionally, the condition is not limited to affluent regions; it is a growing concern in low- and middle-income countries as well, particularly in urban areas where it often exists alongside hunger.[3,4]

Obesity can be broadly defined as a complex disease that occurs when a person's weight is greater than what is considered healthy for a given height, or alternatively, as excess fat accumulation that puts someone at a higher risk for adverse health outcomes.[5,6] Although obesity has long been regarded by the public as a reversible condition based on personal choices, growing research into the many factors that can contribute to obesity suggests that lifestyle is often not enough to cause or prevent obesity on its own. Instead, obesity is becoming increasingly recognised as a chronic condition, and is now regarded as a disease in its own right by well-respected health and medical groups such as the World Health Organization, the American Medical Association, the European Commission and the Canadian Medical Association, among others.

The effects of obesity on human health are varied, impacting an individual's metabolism, cardiovascular system, inflammatory response, and more. These ramifications put those with this disease at a higher risk for numerous serious health conditions and events, such as heart disease, stroke, diabetes, liver disease and cancer. Due to its connection with such serious health outcomes, obesity has, ultimately, been associated with premature mortality — with a study of the United States population finding greater excess mortality for women and Black non-Hispanic adults, surpassing the excess mortality associated with smoking.[7] In fact, obesity-related cardiovascular age-adjusted mortality rates in the United States increased threefold from 1999 to 2020, with the most significant impact seen for Black women.[8]

As obesity rates continue to climb, the wider implications of obesity-related complications for healthcare systems and individuals are becoming more relevant on a societal level than ever. At the same time, investment in research and development for obesity therapies is ushering in a new era of effective medications for this disease. This whitepaper will explore the impact of obesity as a risk factor for a variety of health conditions, how this shapes the treatment of obesity and comorbidities, and how this influences the development of new pharmacological agents, including clinical trials for these agents.

1 billion
by 2030

World's population that will be living with obesity[1]

2.8 million

People die each year as a result of obesity[2]

An overview of obesity

Measuring body fat

Body Mass Index (BMI) is a basic method for estimating body fat, calculated from a patient's height and weight. Like other indices based on parameters readily obtained at office visits, such as waist circumference and waist-to-hip ratio, it can be useful in routine clinical care and in research studies. Although BMI correlates with body fat as measured by imaging modalities, and is associated with increased risk for chronic disease, it has several limitations. It does not distinguish between body fat and lean mass, and it is not as accurate in predicting body fat in elderly patients. The correlation of BMI with body fat also varies with gender and race.[9]

Cross-section imaging with computed tomography or magnetic resonance imaging are the gold standards for the assessment of body composition. In addition to distinguishing between body fat and lean mass, these modalities allow for the assessment of visceral adipose tissue (VAT) versus subcutaneous adipose tissue.[10]

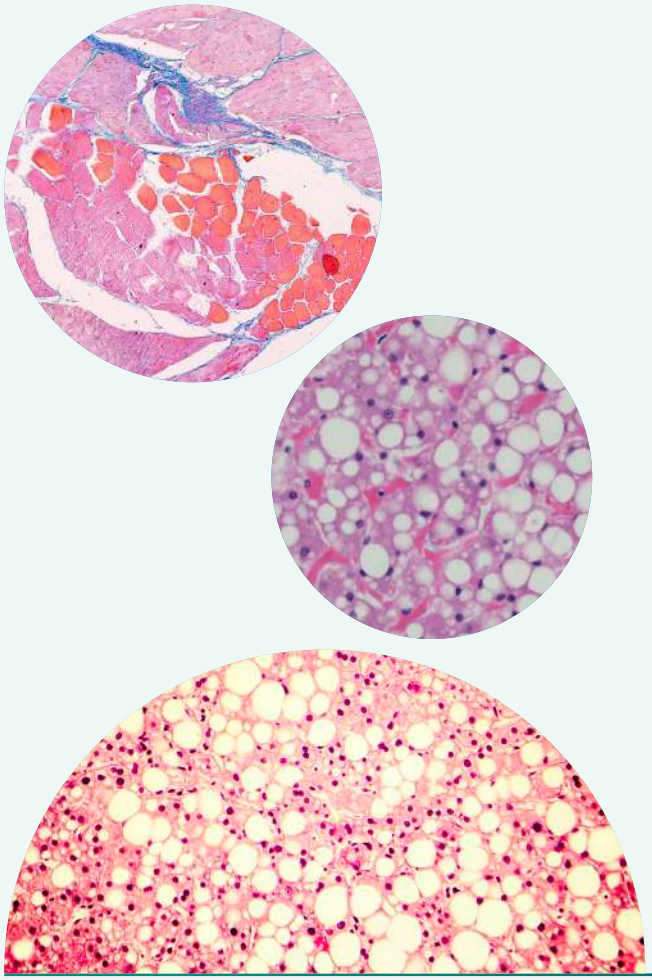
> **Of interest is that VAT is a known independent predictor of all-cause mortality, or risk of death from any cause.[11]**

Dual energy x-ray absorptiometry (DEXA) is the reference standard for the assessment of bone mineral density, and also has utility for body composition assessment. Until recently, DEXA could not measure VAT. However, new software applications provide for VAT estimation, which requires further study.[12]

The biology of obesity

A primary driver of obesity is a surplus of energy intake and a relative deficit in energy expenditure, which forces the body to manage excess energy by either increasing energy storage or energy expenditure. While humans have evolved multiple mechanisms to guard against low blood glucose (i.e., energy deficit), there has not been evolutionary pressure to adapt and guard against the consequences of too much energy in the form of excess sugar, fat or protein (i.e., energy surplus).

When stimulated by a surplus of energy, adipocytes (or fat cells) can rapidly increase in size (hypertrophy) or number (hyperplasia). When adipose tissue progresses into obesity, its rapid growth means the body is not able to deliver sufficient blood supply to all adipocytes, leading to hypoxia and cell death. Macrophages are recruited to these areas of necrosis, where they produce and stimulate the production of pro-inflammatory hormones, such as tumour necrosis factor, interleukin (IL)-6 and leptin.



These hormones induce local inflammation and toxic lipid accumulation, as well as promote oxidative stress, which can damage cellular structures and increase susceptibility to a number of obesity-related complications.

Because adipose tissue is an endocrine organ, an increase in size or number of adipocytes also leads to changes in the secretion of, and sensitivity to, adipokines (cell-signalling hormones secreted by adipose tissue) in ways that can contribute to the development of obesity and conditions associated with obesity.

Our increasing understanding of adipose tissue's role as an endocrine organ, and its impact on and response to hormones, is at the centre of much of the current therapeutic innovation taking place in the field of obesity.

The endocrine function of adipose tissue

The discovery of the fat-derived hormone leptin led to the understanding of adipose tissue as an endocrine organ, as well as how fat-derived hormones signal the body's nutritional state.[13,14] Leptin maintains homeostatic control of adipose tissue mass through neural circuits that regulate food intake and energy expenditure. When fat stores are high, elevated leptin levels signal the brain to decrease hunger and caloric intake and increase energy expenditure. When fat stores are low, the low leptin concentration induces a state of positive energy balance by increasing appetite to restore fat mass.

Leptin mutations in humans are associated with a high degree of obesity and an accumulation of fat in the liver, as well as severe insulin resistance and diabetes.[15] The work of Dr. Elif Oral, which characterised the phenotypes of patients with an abnormal distribution of fat (lipodystrophy), both acquired and congenital, highlighted the importance of leptin expression in metabolism.[16,17] Another study showed that using a leptin analog (metreleptin) to treat health complications caused by leptin deficiency led to marked improvements, correcting hepatic steatosis, reducing insulin resistance and resolving diabetes.[18,19]

Unfortunately, most patients with obesity already have elevated leptin levels and demonstrate leptin resistance. Moreover, leptin treatment does not cause weight loss in most of these patients, although there may be a subset who show some weight loss effect. Investigation of the mechanisms of leptin resistance is ongoing, with the theory that leptin might be particularly important in the maintenance of long-term weight loss.

Gut-derived hormones in obesity

The endocrine activity of the gastrointestinal tract also plays a key role in obesity.[20] Gut-derived, or enteric, hormones influence pancreatic insulin secretion, as demonstrated through the incretin effect: orally administered glucose stimulates a larger pancreatic insulin response than a comparable glucose load given intravenously. Central to mediating this signal is glucagon-like peptide, an incretin hormone.[21]

Studies in 1993 showed that glucagon-like peptide-1 (GLP-1) infusions normalised hyperglycaemia in patients with type 2 diabetes.[22] In addition to augmenting insulin secretion, GLP-1 was also shown to act as part of a so-called "ileal brake," in which nutrient intake is sensed in the ileum, which responds by inhibiting gastric emptying, reducing food intake and inducing satiety. As a result, in addition to being a powerful antidiabetic agent, GLP-1 was identified as an inhibitor of appetite and food intake, indicating its potential use as an anti-obesity agent.

The importance of enteric hormones in addressing obesity is also bolstered by evidence, that many of the results of bariatric surgery are associated with significant increases in gut-derived hormones.[23] Post-surgery changes (such as decreases in appetite, resolution of type 2 diabetes and improved insulin sensitivity) are accompanied by large increases in enteric hormones, including GLP-1, glicentin and oxyntomodulin, as well as product peptide-YY (considered an appetite-regulating hormone). Additional research is exploring the potential role of changes in bile acid signalling and the potential role of changes in the gut microbiome.

Risk factors for obesity

Traditionally, the development of obesity has been attributed to lifestyle choices, with poor diet and sedentary habits at the centre of this viewpoint. Susceptibility to such an energy imbalance has certainly been magnified due to relatively recent environmental factors, such as the increased accessibility and convenience of cheap, calorie-dense foods and the adoption of technology and transportation habits that further reduce physical activity. However, lifestyle alone, cannot explain why some people develop obesity, while others do not. Studies have suggested that the interaction between an individual's environment and their genetics has a significant impact on the development of obesity.[24]

In fact, a large number of genome-wide association studies have found more than one thousand independent loci that can be linked to obesity traits, such as a high BMI or an above-average body fat percentage, with some loci having stronger impacts than others.[24] For example, one study identified 16 genes associated with BMI at statistical significance, with an overrepresentation of genes highly expressed in the hypothalamus, which plays a key role in the neuroendocrine regulation of energy balance. This same study found that rare variants in the GPR75 gene were associated with leanness and protection against obesity.[25]

Lifestyle alone cannot explain why some people develop obesity while others do not. Studies have suggested that the interaction between an individual's environment and their genetics has a significant impact on the development of obesity.[24]

On top of genetic predisposition, parental nutrition is thought to have a role in epigenetic contributors to obesity. A parental history of obesity or food scarcity, among other factors, can change the epigenetics of gametes in ways (such as DNA methylation) that have been associated with the likelihood of obesity in offspring.[26]

Ageing is another factor that can advance obesity for a number of complex reasons. Frequently, lean mass, such as muscle and bone mass, decreases as adults age, while body fat mass increases and is redistributed in the body. Reduced hormone secretion, such as that of growth hormone and adiponectin, is also associated with ageing and correlated with obesity. It has further been suggested that ageing leads to reduced leptin sensitivity (another contributor to obesity) particularly in individuals with higher body fat.[27]

Additionally, various medications can impact weight gain and, consequently, obesity. The use of antipsychotics (such as clozapine, olanzapine and zotepine) has been found to cause weight gain and metabolic syndrome, likely due to their impact on neuropeptides that affect appetite control and metabolism.[28] Another example is corticosteroids, such as prednisone, which are used for anti-inflammatory and immunomodulatory effects. This class of drugs is generally acknowledged to increase the risk for weight gain in adults, with one meta-analysis of corticosteroid use across a variety of indications estimating a 13% prevalence of patients with unintentional weight gain.[29]

The nexus of obesity and comorbid disease

Obesity can influence the function of many physiological systems throughout the body, contributing to chronic disease and other comorbidities. It is becoming clear that there are a number of interrelated factors at play in obesity, including the adaptive and maladaptive metabolic response to energy surfeit; mechanisms such as oxidative stress, local and systemic inflammatory responses; changes in blood flow and perfusion; and the mechanical burden of weight. All of these factors are connected and contribute to the morbidity and mortality of the many and varied obesity-related conditions.

The association between visceral adiposity, insulin resistance, metabolic disease and cardiovascular disease risk can be referred to by many names, including atherothrombogenic syndrome, cardiovascular metabolic syndrome, chronic cardiovascular disease-risk-factor-clustering syndrome and more. The positive caloric balance leading to obesity is associated with adipocyte hypertrophy, VAT accumulation, and other displaced fat deposition, such as in, or around the liver, kidney or heart, leading to abnormal metabolic and immune function that contributes to a broad range of chronic disease and excess mortality.

Inflammation

While the most common clinical presentations of obesity may be cardiovascular or metabolic, it shares many attributes that are common with broader inflammatory disease. There is emerging recognition that many of the health concerns associated with obesity may be linked to underlying inflammatory responses, through the increased secretion of pro-inflammatory adipokines.

One of the hallmarks of obesity-linked inflammation in white adipose tissue (the primary adipose energy storage tissue) is the increased number of macrophages and T helper 1 and 17 cells, and a shift to pro-inflammatory adipokine profiles characterised by increases in tumour necrosis factor, IL-1 beta, IL-6, IL-8 and leptin, as well as, a decrease in anti-inflammatory factors such as IL-10 and adiponectin.

This overabundance of pro-inflammatory adipokines has been associated with a variety of cardiovascular and pulmonary conditions, cancer, metabolic syndrome, diabetes, autoimmune diseases, and gastrointestinal and liver diseases, including hepatic steatosis.[30,31,32]

The body's immune response is altered by this heightened inflammatory state, leading to an abnormal function and activation of immune cells that is theorised to be at least partially responsible for increased susceptibility to, and severity of, infections in obese individuals including respiratory tract infections such as COVID-19.[33] Pro-inflammatory adipokines and systemic inflammation are also linked to the increased likelihood, and possibly even severity, of autoimmune diseases such as autoimmune arthritis and psoriasis in individuals with obesity.[34]

Metabolism

Obesity is an identifying characteristic of metabolic syndrome, a cluster of conditions (abdominal obesity, high blood pressure, high blood sugar, high blood triglycerides and low levels of high-density lipoprotein cholesterol) that greatly increases the risk of heart disease, stroke and diabetes and has been connected to a variety of other health concerns. Metabolic syndrome has been associated with the increased risk of pancreatic cancer, as well as liver and gastrointestinal conditions such as non-alcoholic fatty liver disease (NAFLD) and gastroesophageal reflux disease.

Current evidence supports that dyslipidaemia (an imbalance of lipids in the blood) associated with obesity and adipose dysfunction may be an immediate cause of insulin resistance. This is clearly a driver and risk factor for type 2 diabetes mellitus, a known independent risk factor for cardiovascular disease and associated with hypertension and hyperuricaemia. Further, the insulin resistance associated with obesity reduces renal urate excretion, which increases the risk of gout. In fact, the relative risk of gout in men increases stepwise with increasing BMI.[35] Because insulin resistance is frequently found in those with metabolic syndrome, it is considered by many to be a key feature, and potentially even a cause, of the condition.

Cardiovascular system

Many of the physical alterations caused by obesity can have a direct impact on the cardiovascular system. For example, the pro-inflammatory state of obesity has been linked to the development of atherosclerosis and the destabilisation of atherosclerotic plaque, with the multiple innate and adaptive immune responses associated with atherosclerosis, a subject of ongoing investigation. Additionally, higher levels of adipose tissue can often lead to hypertension and ventricular enlargement for individuals with obesity.[36]

Obesity further impacts the cardiovascular system indirectly. It can, for instance, increase the risk of obstructive sleep apnea, which is potentially caused by the effects of fat deposits on the airway anatomy and leads to fragmented sleep patterns.[37] Fragmented sleep is well established to raise pro-inflammatory markers and is associated with an increase in coronary risk and hypertension, among other conditions. Other examples include the hyperglycaemia of diabetes, which can damage the heart and blood vessels, and obesity's increased risk of dyslipidaemia, which can cause plaque buildup in arteries and increase the risk of heart attack.

Another consequence of obesity is the increased risk of thrombotic disorders such as stroke, myocardial infarction and venous thromboembolism. This is due to the upregulation of circulating procoagulant factors and downregulation of anticoagulant factors, as well as an increase in platelets, in addition to proteins that inhibit the breakdown of blood clots.

ICON survey results

The indications most commonly included in respondents' obesity-related research include:

Indication	Percent
Diabetes	55%
Metabolism / metabolic diseases	48%
Mental health	39%
Cardiovascular diseases	38%
Obesity only / core obesity research	37%
Inflammation and inflammatory diseases	26%

Addressing obesity's comorbidities

While these comorbidities are serious, evidence has found that weight loss can mitigate these negative health effects. Modest weight loss (6% at study end), achieved with intensive lifestyle interventions, can lead to improved cardiometabolic parameters in individuals with diabetes mellitus.[40] A weight loss of 10% or more has been linked with a reduction in cardiovascular disease, such as through bariatric surgery or treatment with a GLP-1 agonist.[41,42,43] The loss of at least 15% of body weight is correlated with better glycaemic control, the decreased likelihood of cardiometabolic disease, and an improvement in overall quality of life.[44]

As a result, the clinical importance of developing safe and effective medical therapies for weight loss and treatment of obesity (without the invasiveness of surgery) has become incontestable, based on the growing global epidemic of obesity and obesity-related morbidity.

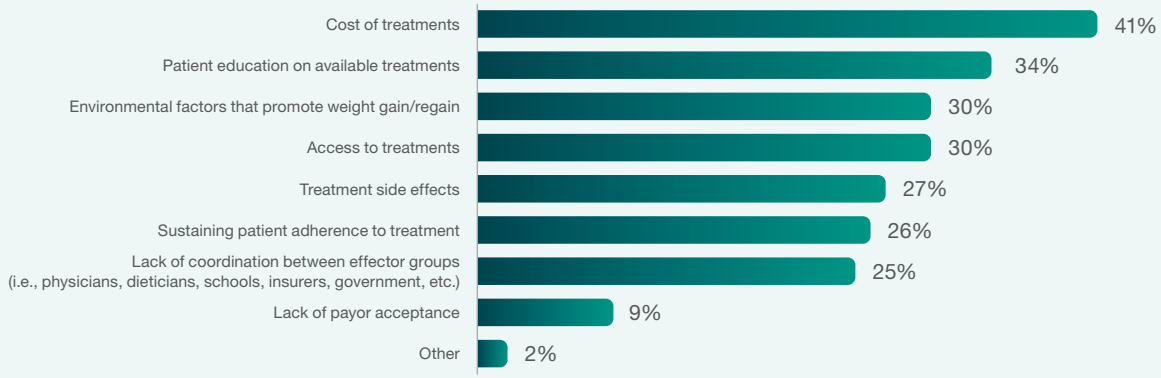
Interconnection between obesity and mental health

The connection between obesity and mental health is complex, and bi-directional. The psychosocial pressures and stigma associated with obesity can lead to depression, eating disorders and anxiety, among other mental health impacts.[38]

However, it is well known that many mental health conditions, such as generalised anxiety disorder and depression, can be associated with significant weight gain as part of the underlying condition.[39]

What do you see as the biggest barriers to reducing obesity in the general population?
(Please select up to three barriers)

Key barriers to reducing obesity in the general population

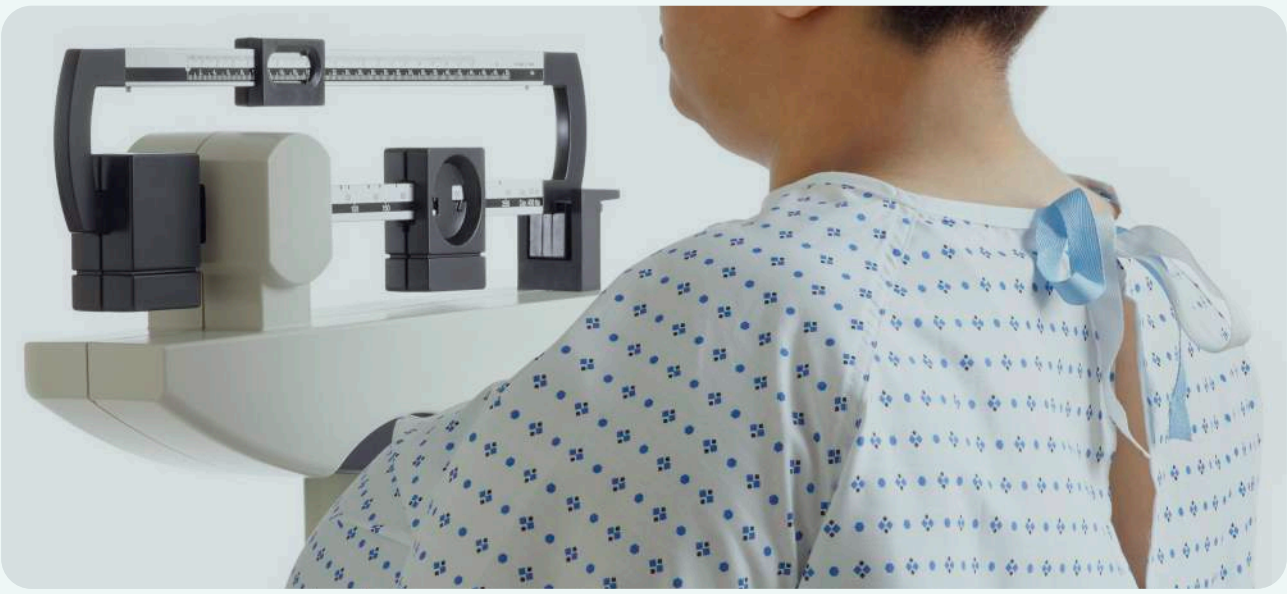


Base: All respondents; up to three answers permitted (n=104)

ICON survey insights

- Concern regarding cost of treatments as a key barrier to reducing obesity is primarily driven by respondents working in large pharma (34%), as opposed to those in large biotech (0%).
- Selection of 'sustaining patient adherence to treatment' as a key barrier to reducing obesity significantly increased over the course of the survey. This shift may have been influenced by concurrent media coverage of pharmacological obesity treatments and an evolving public understanding of the potential benefits of weight loss on long-term complications.

Treatment of obesity and associated conditions



Historical context of obesity treatment

Obesity treatment has a long and storied history that has included a variety of approaches to weight loss, dating back to ancient Greece. Modern pharmacological treatment of obesity ostensibly began in the 1940s and '50s, relying on sympathomimetics, primarily amphetamines and amphetamine derivatives, to increase resting energy expenditure and decrease appetite. However, this class of drug carried concerning health risks, such as the potential for addiction and abuse, and negative impacts on the cardiovascular system, leading many of these treatments to be removed from common usage for weight loss. A prominent example from the 1990s is the use of the combination of phentermine and fenfluramine, referred to as phen-fen. This treatment was associated with primary pulmonary hypertension and heart-valve disease, and led the FDA to request phen-fen's withdrawal from the market.

In 1991, a National Institutes of Health-sponsored consensus development conference acknowledged the success of bariatric surgery to decrease weight, resolve insulin resistance and cause remission of type 2 diabetes, and released recommendations for the consideration of bariatric surgery in certain patients with obesity. Originally, it was thought that the surgery reduced weight due to malabsorption of nutrients or calorie restriction. However, post-surgery weight loss was found to be more related to decreases in appetite, as well as a comparatively higher resting metabolic rate, than seen with weight loss from low-calorie diets. Further, findings that the positive impact of bariatric surgery, specifically on diabetes and insulin sensitivity, occurred days after surgery, which was well before the onset of significant weight loss and suggested complex factors were at play. This led to the discovery of the role of enteric hormonal signalling in obesity and related conditions, which, in turn, steered obesity drug development in a new direction, including toward the use of GLP-1 receptor agonists. The recognition of the hormone oxyntomodulin is of particular interest as this provides the basis of emerging dual and triple agonist therapies in the current obesity treatment landscape.[45]

Current approaches to obesity treatment

Various health organisations have recommended their own sets of guidelines for the clinical treatment of obesity. One was jointly published in 2013 by the American College of Cardiology, the American Heart Association and The Obesity Society, and another released by the American Association of Endocrinologists (AACE) and the American College of Endocrinology (ACE) in 2016, agree on many points.[46] These include that individuals with obesity and obesity-related complications should lose at least 5% of their body weight, with an emphasis on increased aerobic activity, a reduced calorie diet and a behavioural lifestyle intervention, all individualised to the patient. The AACE/ACE guideline specifically notes that lifestyle therapy can be combined with pharmacotherapies should lifestyle therapy prove ineffective on its own.

Other guidelines add further nuance to approaching clinical treatment. The guidelines established in 2015 by the Obesity Management Task Force of the European Association for the Study of Obesity note that the aim of obesity treatment should include quality of life, reduction of health risks and body composition, in addition to weight loss — and that treatment of obesity comorbidities should be considered to be a part of treating obesity itself.[47] Furthermore, the guidelines released by Obesity Canada and the Canadian Association of Bariatric Physicians and Surgeons (2020) focus on the patient journey, which should involve the discussion of treatment options, agreement regarding goals of therapy, and follow-up and advocacy.[48]

None of these guidelines are comprehensive, as the field of obesity treatment is continuing to grow and evolve. For instance, many of these guidelines were released before several major obesity treatments were granted regulatory approval. As such, clinical standards of obesity treatment must evolve alongside the science — which is increasingly supporting the concept that treating obesity frequently requires more than just lifestyle changes.

To date, bariatric surgery is the most potent treatment for obesity, and is associated with long-term weight loss of up to 25% after five years, with effects that may persist for up to 20 years post-surgery. Multiple long-term studies have consistently shown that the most common procedures (sleeve gastrectomy and Roux-en-Y gastric bypass) produce superior weight loss compared to alternative, nonoperative therapy. Substantial clinical evidence supports the benefits of bariatric surgery in all aspects of obesity-related metabolic dysfunction, and it has been found to decrease mortality from cardiovascular disease or cancer by 30% and 23%, respectively.[49]

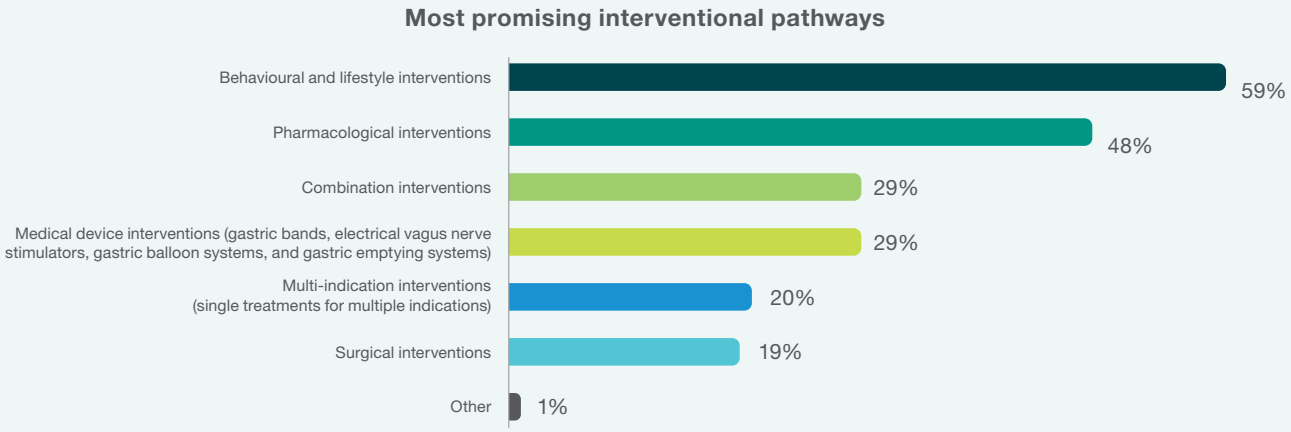
Given that regulators have agreed that 5 - 10% weight loss is sufficient to have a beneficial effect on obesity-related metabolic co-morbidities, American and international societies for bariatric surgery have recommended bariatric surgery for those with a BMI of 35 or greater, or those with type 2 diabetes and a BMI of 30 or greater. Due to its success and widespread promotion, bariatric surgery has set expectations for nonoperative therapies as well, both in terms of patient expectations for weight loss, and payor and insurer expectations of potential medical benefit.

Pharmacological intervention is an important option for obesity treatment. There are at least two broad approaches to pharmacological weight loss: 1) decreasing caloric intake by affecting appetite through satiation and slow caloric absorption, and 2) increasing metabolism to burn more calories. Some classes of drug can function in both of these categories, as in the case of sympathomimetic therapies, such as phentermine. As our understanding of the mechanisms underlying obesity improve, the resulting pharmacological solutions have grown more complex and effective.

ICON survey results

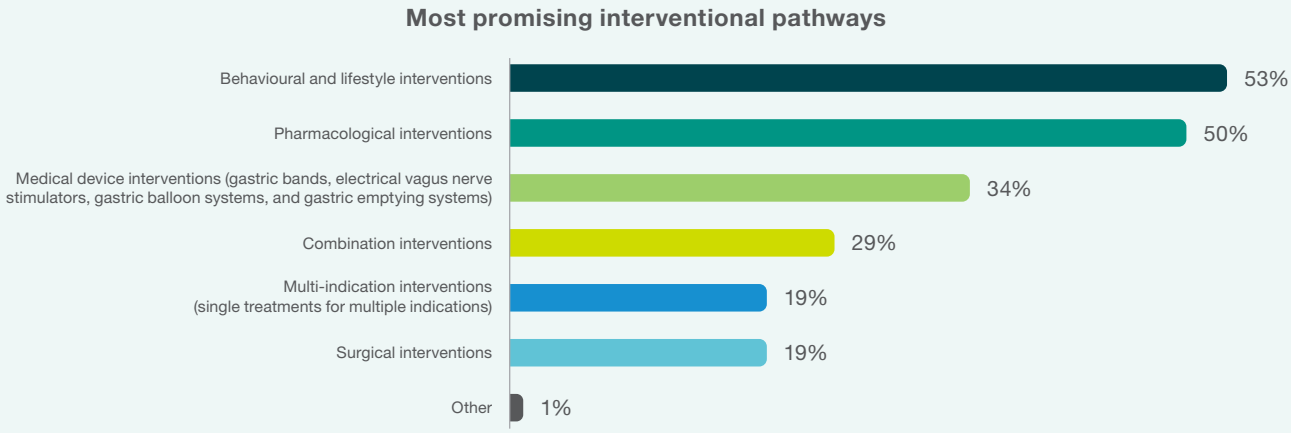
The most promising current interventional pathways to preventing rising obesity rates among the general population are, behavioural and lifestyle interventions (59%) and pharmacological interventions (48%). 29% of respondents most often use these 2 interventional pathways in a combination intervention approach.

Which of these do you think are the most promising interventional pathways to prevent rising obesity rates among the general population? (Please select up to three pathways)



Base: All respondents; up to three answers permitted (n=104)

Which of these do you think will be the most promising treatments for obesity in the future? (Please select all that apply)



Base: All respondents; up to three answers permitted (n=104)

Advancing pharmacotherapies in obesity

Recently, there have been significant advances in the pharmacological treatment of obesity. One of these has been the regulatory approval or fast track designation of several GLP-1 receptor agonists, such as semaglutide and tirzepatide (which acts dually as a glucose-dependent insulinotropic polypeptide [GIP] agonist that stimulates pancreatic insulin production), as appropriate for use in treating obesity.

GLP-1 agonists are currently considered one of the most powerful anti-obesity agents, most recently demonstrating reductions in the risk of cardiovascular and renal complications associated with obesity.[50,51] By binding to GLP-1 receptors, the agonist promotes insulin secretion and synthesis (important to the proper absorption of glucose in the bloodstream) as well as, slowing gastric emptying and reducing appetite.

Primarily approved for use in the treatment of type 2 diabetes, these drugs have also been found to be beneficial in treating obesity. Effectiveness studies on semaglutide, for example, have demonstrated a 14.9% loss of body weight over the course of 68 weeks in patients with obesity who do not also have diabetes. This is compared to a 2.4% weight loss with placebo.[52] And tirzepatide has shown great promise in patients with obesity and type 2 diabetes, with a higher percentage of participants achieving at least 5% body weight loss when taking tirzepatide over placebo, basal insulin, or a singly acting GLP-1 receptor agonist.[53]

There is also a wealth of obesity treatments currently in clinical trials, which indicate potential directions that pharmaceutical intervention may take in the future.[54] Several new GLP-1 receptor agonists are under investigation, individually as well as in combination with other mechanisms, such as GIP and glucagon agonists. Developing small molecule, orally effective agents in the GLP-1 receptor agonist class is a particularly compelling avenue, as these may alleviate the need for injection. Amylin, which signals satiety and slows gastric emptying, is another hormone of interest, for which researchers are exploring the potential of analogues and receptor agonists. There is also interest in the use of tocotrienols to increase expression of adiponectin and, as a result, aid in addressing insulin resistance. While these are only a sample of anti-obesity medications in development, the overall trend is in promoting appetite reduction and satiety.

As the medical field moves forward into a new era of treating obesity and related conditions, it becomes necessary to consider where the gaps are in current treatment and what is needed to ensure the continued health of patients who receive these treatments.

Finding long-term therapeutic solutions

Maintaining weight loss and overall weight maintenance in the long term is necessary to ensure health benefits. For example, improvements in glucose, insulin and blood pressure that come with weight loss have been shown to revert to the baseline with even mild weight regain.[55] Sustained commitment to obesity management must be an ongoing process to achieve desired health outcomes, and it is not by any means a simple endeavour.

Weight is monitored and controlled by the body and brain, based on a variety of signals (such as hormones) and systems, which, together, create a kind of "weight set point" that is physiologically defended but which can also change, creeping higher as patients age, and tending to cause weight regain after weight loss. By some estimates, patients who lose weight through lifestyle changes can expect to gain back approximately 80% of lost weight within five years.[56]

Sustained commitment to obesity management must be an ongoing process to achieve desired health outcomes.

Pharmacological interventions face similar difficulties. Current medications are aimed at controlling energy intake and expenditure, and although some newer hormonal agents do synergise with healthy life habits, there are no available therapies that address weight regain mechanisms, leaving few options but continual usage. For example, within two years after discontinuing the use of semaglutide for obesity management, patients regained two thirds of the weight they initially lost from using the drug.[57] However, some studies suggest that with continual ongoing use of medication, patients can maintain weight loss of 10% or greater for more than four years.[58] Future research will likely investigate whether therapies based on weight set point arbiters might be used for maintenance.

Bariatric surgery has generally achieved long-term efficacy, with most patients who undergo gastric bypass or gastric band surgery maintaining their weight loss over the course of years.[59] Unfortunately, bariatric surgery can be more invasive than many patients would prefer, and it is only recommended for a limited subset of patients with obesity. Due to the alteration of the digestive tract, it can also be accompanied by reduced intake or malabsorption of nutrients, leading to complications, such as anaemia, vitamin deficiencies and protein malnutrition.

The potential of multidisciplinary and combination therapies

Due to the complexity of obesity as a disease, and the difficulties inherent in maintaining weight loss, in many cases one single solution is not enough. Instead, it may require a blend of different approaches or medications to affect the desired outcomes for a patient.

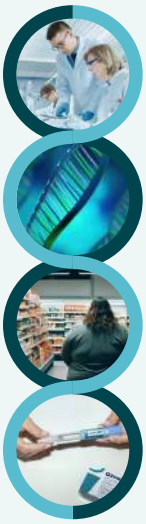
Multidisciplinary therapies involve multiple medical disciplines working together to achieve a common goal. For obesity, this may mean bringing a team of physicians, dietitians, exercise specialists, behavioural therapists and other relevant professionals to create an individual's obesity treatment plan for optimal results. Such multidisciplinary approaches can have a significant impact, as in the case of patients taking anti-obesity medications who also receive ongoing support through healthcare providers and lifestyle counselling. Compared to treatments that end after a short period of time, continued interaction with healthcare providers or group settings improves long-term outcomes for those attempting to maintain weight loss.[56]

Combination therapies may employ multiple drugs to increase efficacy of treatment. This can mean using multiple anti-obesity medications that have different mechanisms of action, such as the use of dual incretin agonists given as separate drugs, or combining an anti-obesity medication with one approved for a separate indication, but with potential to aid in weight management.

A common example of the latter is when patients with diabetes use metformin or sodium glucose cotransporter-2 inhibitors, which are indicated for diabetes but also help in weight loss, in combination with targeted weight loss drugs. Furthermore, pharmacotherapeutics can be combined with bariatric surgery to help prevent weight gain. The advantage of such combinations is that they allow a more optimised treatment for patients who do not respond well to a single treatment. However, there are multiple factors that need to be taken into account when considering combination or adjunctive therapy approaches, one of which is the potential for drug-drug interactions from a pharmacokinetic and a pharmacodynamic standpoint.

ICON survey results

The areas most commonly included in respondents' obesity-related research include:



Clinical research	**39%**
Genetics and epigenetics	**36%**
Effects of diet on obesity and overall health	**33%**
Pharmacologic and device therapies	**33%**

Clinical trial logistics

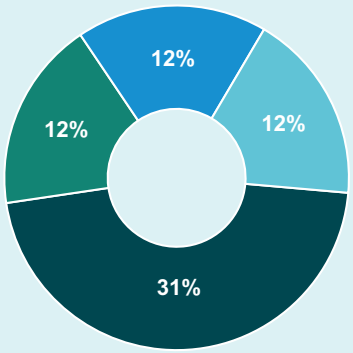
The recent approvals for GLP-1 receptor agonists (both singly and as a dual agonist, as in the case of tirzepatide) for obesity treatment are changing the field. These approvals were facilitated by two decades of clinical experience with GLP-1, coupled with breakthrough results showing improvements in cardiovascular disease and renal mortality — all of which have allowed regulators to consider the potential risks and benefits of treating people with obesity with hypoglycemic agents, even if they do not also have diabetes.

Such dramatic shifts in the obesity treatment landscape means that development pathways for new obesity drugs are shifting as well. While this area is still evolving, there are a number of important considerations for obesity-related trial design and execution.

Challenges in obesity related development

Survey respondents ranked clinical trials as the most challenging aspect of obesity-related drug or device development. Clinical trials received 31% of votes, well above other challenging areas of development, including drug discovery (12%), preclinical studies (12%) and regulatory approval (12%).

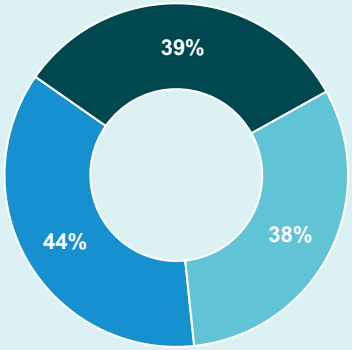
Most challenging aspect of obesity-related drug/ device development



- Clinical trials
- Drug discovery
- Preclinical studies
- Regulatory approval

Among the challenges specific to obesity-related clinical trials, the three that respondents viewed as most challenging were lack of long-term follow-up (44%), lack of obesity-appropriate trial designs (39%) and difficulty recruiting diverse populations (38%).

Specific clinical trial challenges



- Lack of long-term follow-up
- Lack of obesity-appropiate trial designs
- Difficulty recruiting diverse populations

Recruitment and retention

Recruiting diverse and representative study populations

Enrolling a diverse participant cohort in clinical trials that is representative of the targeted patient population is always a central concern of clinical trials, and an area of growing regulatory scrutiny. Clinical trials operate in a highly controlled environment with strict inclusion and exclusion criteria. It is, therefore, imperative to ensure that the efficacy and safety of a pharmacotherapy is generalisable to the broader population it is intended to treat. Without a clear and well-defined strategy, it is highly likely that certain demographics may be vastly over- or underrepresented in a study.

This is equally true for obesity clinical trials, which tend to enrol large proportions of white women. This demographic is generally overrepresented in clinical trials related to obesity and weight loss, vastly outnumbering men and people of non-caucasian ancestry.

Nevertheless, making a targeted effort to recruit among underrepresented populations can make a significant positive impact. For example, when no efforts were made to target any specific demographic for one weight loss trial, women, in general, represented 85.7% of participants, with non-Hispanic white participants at 87.5%. When targeted efforts were made for that same trial, those numbers fell to 50.4% women and 52.8% non-Hispanic white participants.[60]

ICON survey results

Factors with the greatest potential to improve patient population diversity in obesity-related clinical studies

Respondents believe that **reducing patient burden (33%) and monetary patient incentives (30%)** are the factors most likely to improve the diversity of patient populations during the clinical trial recruitment.

Despite similar rates of obesity across gender, men are estimated to make up only about one quarter of participants in weight loss trials.[61] This may be because men are less likely to take protective health behaviours, such as seeking medical, psychological help or participating in health programmes.[60]

Targeted placement in the local media is one method that has been shown to garner interest from men. One study focused on weight loss intervention for men, found that one week of newspaper advertisement resulted in the recruitment of nearly twice as many men as worksite recruitment, newsletters, social media and recruitment posters combined, while local sports radio advertisements have also been effective at attracting male interest.[63,60] On top of targeted placement, the content of recruitment materials should be focused as well. For example, images of men in leadership roles with a positive tone and captions under 35 words have been found to be most successful for visual advertisements.[62]

Obesity is also a serious concern across racial and ethnic groups. According to the CDC, 49.9% of non-Hispanic Black adults and 45.6% of Hispanic adults are affected by obesity, compared to 41.4% of non-Hispanic white adults.[64] Nonetheless, as noted above, these groups are often underrepresented in obesity trials. Therefore, it is vital to take measures to ensure that these groups are sufficiently represented in clinical trials.

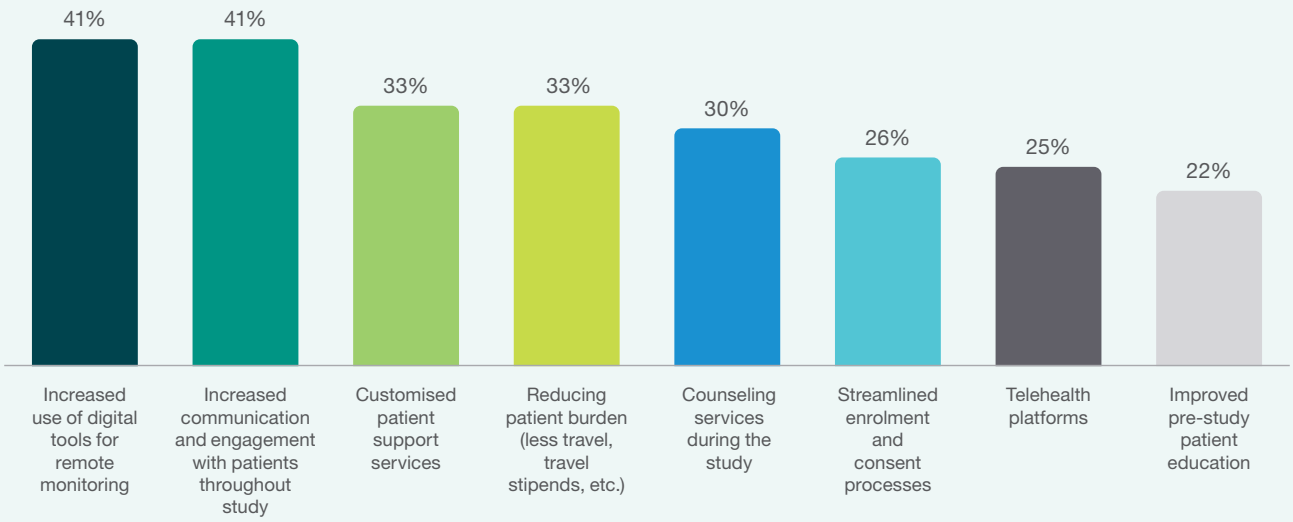
Common methods for recruiting racial and ethnic minorities include leveraging health centres in areas with high minority populations, as well as including language and imagery specific to these groups in recruitment messaging. For obesity-related trials, technology also provides several promising approaches. Tailored emails sent to individuals identified through electronic health records have shown some success in recruiting Black women to weight loss trials.[65] Meanwhile, racial minority enrolment tends to be higher in weight loss clinical trials that incorporate a smartphone element.[66]

A further consideration is diversity of body weight and composition. The inclusion/exclusion criteria for many clinical trials place an upper limit on patient BMI, largely due to concerns about the impact of pharmacokinetics on drug dosing. However, when individuals with obesity can reasonably be expected to use a given treatment, studies should include an appropriate diversity of body weights and BMI. Because adipose tissue has different pharmacokinetic properties than lean tissue, and because individuals with higher weight have been shown to have different metabolic profiles, it should not be assumed that a drug will function the same way for patients of all weights.[67] Lack of diversity in body weight in research means that a treatment may not act as intended for individuals whose BMI does not fall within a trial's inclusion criteria. As such, inclusion/exclusion criteria should be considered very carefully, especially in light of the intended clinical population.

Considering paediatric trials

While obesity rates for children continue to rise, the number of anti-obesity treatments approved for paediatric patients remains limited. Obesity and obesity-related conditions may have a different physiology for children, particularly those who have not yet hit puberty. For example, children can develop a different phenotype of NASH than seen in adults, meaning that the treatments adults receive may not be applicable. Sponsors should carefully consider whether paediatric trials are appropriate and, if so, carefully plan them to account for differences in this population, such as the impact of physical maturation on physiology, the decreased accuracy of BMI for determining obesity in children, and challenges for recruiting and engaging children and their caregivers.

Which of the following do you think could have the greatest impact on improving patient recruitment in obesity-related clinical studies? (Please select up to three factors)



Base: All respondents; up to three answers permitted (n=104)

Challenges in retention and confounding variables

Once trial participants have been recruited, the next challenge is keeping them engaged. Obesity clinical trials have a number of distinct challenges for patient engagement and retention alongside typical barriers such as travel to study sites.

Some of these challenges lie in the physical impact of the obesity treatment being tested. Gastrointestinal side effects such as nausea, vomiting and diarrhoea are common across multiple obesity therapies. Such side effects may be deemed too unpleasant by clinical participants and lead to their exiting the trial — meaning that proactive strategies are needed to mitigate this challenge, such as patient education on the investigational product or provisions for investigational product restart after temporary discontinuation. Additionally, because changes in weight are often easily discerned by the patient, it can become clear early in the study whether that patient has been receiving a placebo. If participants receiving the placebo are not achieving any significant weight loss, they may choose to disengage from the study.

The length of time needed for follow-up also presents difficulty for patient engagement. As noted previously, obesity requires long-term solutions, which necessitate long-term follow-up to ensure safety and continued efficacy. Maintaining patient engagement over this period can require measures beyond what might typically be employed in a shorter trial. One option is digital health technology, such as wearable devices and remote data collection, which can allow participants to engage with the study remotely, rather than depending solely on site visits. Another is to utilise adherence reminders and/or check-ins to keep the clinical trial fresh in the minds of participants.

A final factor to keep in mind: traditional media and social media can influence patient behaviour, possibly impacting trial results. Commonly, traditional media, such as movies and television, idealises thinness and minimises the biological and systemic factors that play into obesity, instead ascribing body weight primarily to personal lifestyle choices.[68] Similarly, social media promotes ideals of thinness, stigmatises overweight and obesity and enables body comparisons that lead to self-image dissatisfaction for users.[69] The effects of this can be detrimental to patients and researchers: exposure to stigmatising content has been shown to increase caloric consumption by overweight individuals, with stigma even leading to poorer outcomes for those enrolled in weight loss programmes.[70,71] It is therefore important to account for this potential influence on participant behaviour during clinical trials.

> **Obesity requires long-term solutions, which necessitate long-term follow-up to ensure safety and continued efficacy.**

ICON survey results

The factors believed to have the greatest positive impact on patient retention in obesity-related clinical studies include:

Customising scheduling to suit patient's timing	**36%**
Customised patient support services	**33%**
Reducing patient burden (less travel, travel stipends, etc.)	**32%**
Monetary patient incentives	**31%**
Increased communication and engagement with patients throughout study	**26%**
Engaging and including patient family members in patient advocacy	**24%**
Engaging with obesity advocacy groups for support services	**23%**

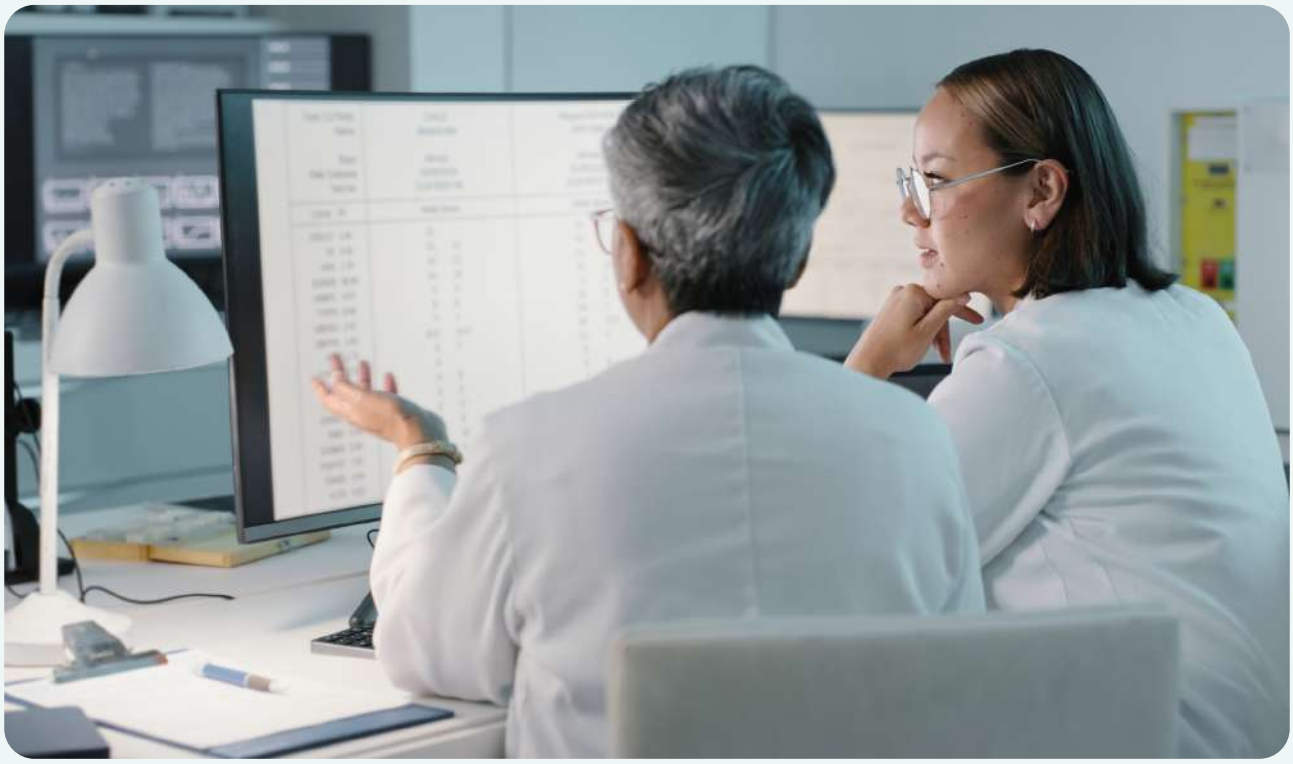
Case Study: Patient retention in a GLP-1 RA trial

Challenge: ICON supported a cardiovascular outcome trial for a GLP-1 receptor agonist, enrolling more than 9,900 patients with type 2 diabetes. The treatment phase of the study spanned approximately seven years from the first patient randomised to the last patient visit. Retaining patients for this length of time required proactive measures from study start to study completion to ensure data integrity and the success of the trial.

Solution: ICON proactively implemented a tripartite approach to maximise patient retention at study initiation consisting of 1) site outreach and patient engagement; 2) real-time patient tracking and risk classification; and 3) systematic mitigation strategy. Site and patient-specific retention strategies were key measures to ensure the selection of experienced sites, long-term engagement of patients and dynamic site response to retention challenges.

Risk-based monitoring was used to trigger additional monitoring of sites identified as meeting predefined retention risk indicators. A dedicated retention team, working in collaboration with a clinical operational team was employed to prevent, detect and correct patient retention issues in conjunction with monitors and sites throughout the study. Through a systematic mitigation process flow and intervention pathway, patient adherence to the study drug and regular study contacts were achieved at maximum potential. Proactive retention strategies included patient education on the investigational product, and proactive provisions for investigational product restart after temporary discontinuation.

Outcome: Through the use of a multi-pronged proactive retention strategy, less than 1% of participants were at risk for becoming lost to follow-up at the commencement of the final study visits. At study completion, nearly seven years from the first randomised patient, greater than 97% of patients completed the trial.



Clinical trial design

Master protocols

When bringing a therapy to clinical trials, sponsors must consider how best to optimise the study design efficiencies. In the past, asset development has often proceeded from diabetes to weight loss and/or NASH indications. For these obesity-related conditions, the use of master protocols may be particularly useful to allow for the simultaneous development of an asset for multiple indications. Master protocols are specifically constructed to test multiple hypotheses and may include parallel sub-studies, but have an overarching set of procedures to improve efficiency. These efficiencies might include a common screening protocol and potential sharing of control subjects. Examples of designs that employ master protocols include basket trials and platform trials.

Basket trial design is well suited to account for the interconnected therapeutic areas found within obesity-related comorbidities. This trial design allows a treatment to be tested on multiple indications or subtypes of a single disease which have a common molecular characteristic. An example of a basket trial would include the testing of one drug's ability to treat a group (or "basket") of obese patients with different genetic variants on the same one or two alleles.[72]

There are two main approaches to basket trials: 1) testing within a subtype of one disease, or 2) testing across a diverse span of diseases, which all share a commonality. In the case of obesity treatment, for instance, this might allow sponsors to test a drug's efficacy across obesity, diabetes and liver disease all within one basket. Such a design allows patients to be funnelled into the trial that best fits their specific disease expression.

Further, it allows researchers to tailor treatments to a particular patient profile, thereby enabling specific and personalised treatment plans for a given disease expression. For example, some agents, such as integrin mimetics, can be used across a broad swathe of patient profiles with different durations, dosages, and the like. A basket trial could potentially help determine what durations and dosages are beneficial for a specific patient profile.

Platform trials utilise master protocols to evaluate and compare multiple interventions for one indication through multiple trial arms. These trials are adaptable, allowing researchers to begin additional arms or evaluate results of an arm while the trial is ongoing. This design can facilitate the development of different assets for the same indication, as it provides a pre-established framework for bringing these assets to trial. Because a platform trial enables evaluation at intervals throughout the trial, it allows sponsors to focus efforts on the most promising assets while dropping trial arms with treatments that prove to be ineffective, thereby conserving resources. Moreover, a platform trial requires a lower sample size (compared to several individual studies), but allows a greater percentage of trial participants to receive treatment, since only one arm of several needs to receive placebo.

Because a platform trial enables evaluation at intervals throughout the trial, it allows sponsors to focus efforts on the most promising assets while dropping trial arms with treatments that prove to be ineffective, thereby conserving resources.

Patient-centric design

A key element to any clinical trial design is integrating patient centricity. One facet of this is understanding the patient journey and ensuring that each part of the process keeps the patient's needs in mind. Study start-up should be streamlined from the patient perspective, including through easily accessible and understandable patient education and processes such as e-consent. Consistent communication and engagement with patients throughout the trial support their participation. Finally, providing lay summaries after the conclusion of a trial provides participants with an understanding of the research and findings to which they have contributed. Such summaries can broaden the impact of research by making it accessible to a larger audience.

Hybrid and decentralised clinical trials (DCTs) often contribute to patient centricity as well, by decreasing the burden of participation. Given the relative ease of determining eligibility using common measures such as height and weight, DCTs enable patients to self-refer into studies through the use of online self-screening tools, making it easier for invested individuals to take part.

DCTs can significantly reduce patient burden through the reduction or elimination of travel to a centralised location, which can be time-consuming and present difficulty for those who lack transportation. DCT's use of digital tools, such as heart rate monitors or smartphone applications, makes it easier for participants to stay engaged, with less effort required for patients and researchers to collect data.

Long-term follow-up

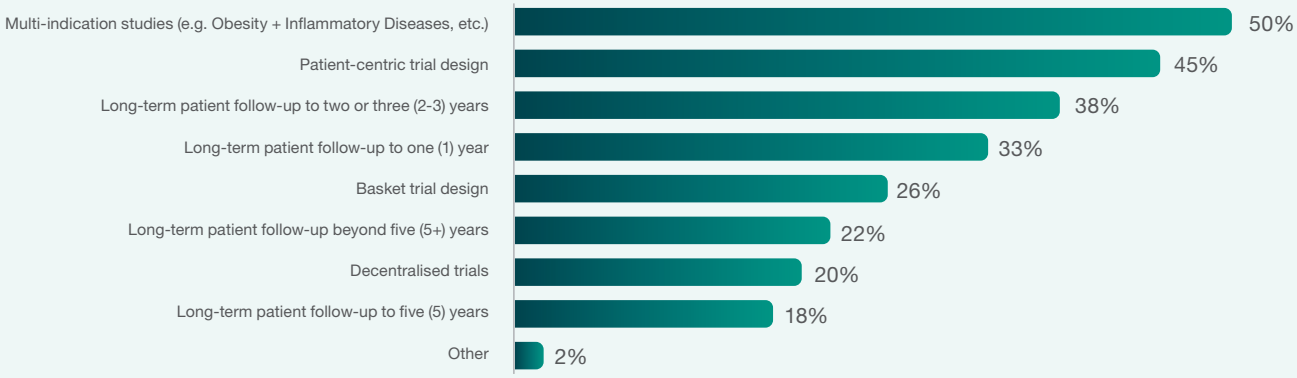
Continuing follow-up to gather data in the long term is a common requirement for many indications, obesity among them. Long-term safety is a concern: as noted previously, there is a history of negative health impacts from obesity drugs, making it crucial to monitor for any potential risks. This necessitates long-term data on the duration and dosage of treatments, particularly when considering relatively new drugs, such as semaglutide, which may not have been in use for obesity treatment long enough to gather comprehensive data on outcomes and safety. Regulatory bodies require some degree of long-term safety monitoring. For instance, the FDA currently requires basic cardiac safety monitoring to be conducted for obesity treatments. However, in addressing obesity there are compelling reasons for long-term follow-up over and above the required basic safety monitoring.

The first is the need to understand the requirements for maintaining weight loss. Maintenance of weight reduction is regarded as one of the biggest challenges in obesity management, and learning what is needed for long-term maintenance is a key consideration in the treatment of obesity. Long-term data is necessary to better understand what is required, and what factors may affect weight maintenance for patients undergoing a given treatment.

Second, long-term studies can help to determine whether a treatment can benefit other hard obesity-associated clinical endpoints, including major adverse cardiovascular events (MACE), congestive heart failure, chronic kidney disease and the onset of diabetes. Because obesity is so closely connected with such health events, treating obesity may reduce their occurrence, and long-term data is important to determining a treatment's impact on them. Having this information can contribute to the marketability of an obesity treatment compared to potential competitors that have already proven to have outcome benefits.

Novo Nordisk's SELECT trial provides an excellent example of the benefits: The primary endpoint of SELECT — a five-year, double-blind, parallel-group, placebo-controlled study evaluating weekly subcutaneous injections of Wegovy® (semaglutide, a GLP-1 receptor agonist) in non-diabetic patients with a history of cardiovascular disease — was the reduction of MACE.[73] In August 2023, Novo Nordisk reported a 20% reduction in MACE compared to placebo, outpacing the 15-17% reduction analysts had been expecting, and boosting Wegovy's® prospects clinically and financially. And, Wegovy® is not alone, as a number of other GLP-1 receptor agonists have had positive cardiovascular outcome trials in patients with diabetes.

Which of the following design components are you currently employing in your obesity-related clinical studies? (Please select all that apply)



Base: All respondents; multiple answers permitted (n=104)

The design components most likely to be employed in respondents' obesity-related clinical studies are:

Multi-indication studies

Patient-centric trial design

Researchers should also make certain to include patients with obesity in long-term follow-up studies for treating related indications, such as cardiovascular disease and NASH. Because a body's ability to metabolise and excrete a drug, as well as the volume of distribution of a drug within the body, can be impacted by body composition, ascertaining a drug's ongoing safety and efficacy over time for patients with obesity is paramount, particularly in indications that are closely linked with obesity.

Post-market follow-up is another significant consideration. While phase 3 clinical trials for obesity treatments are recommended to have a duration of one year for FDA approval, this timeframe is likely not sufficient to gather comprehensive, long-term efficacy and safety data. As a result, gathering real-world population data in the long term after trials have ended is an invaluable course of action.

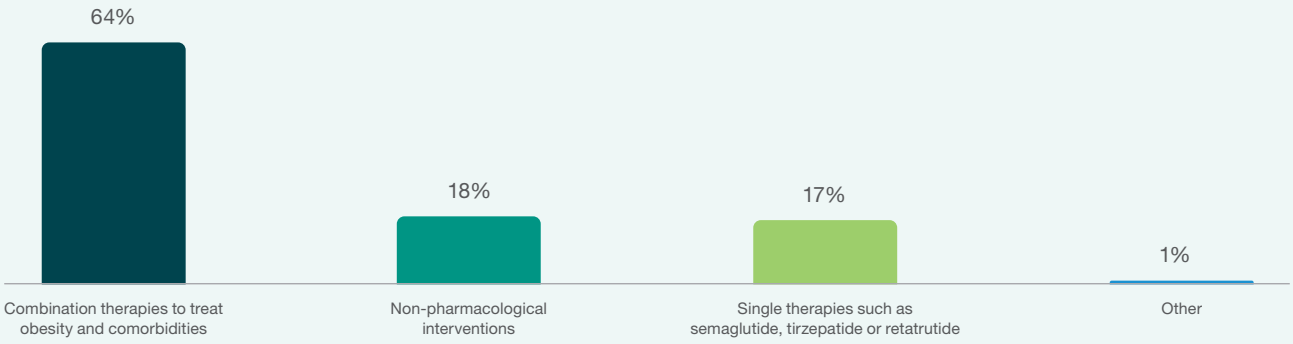
One way to collect this data is to utilise clinical trial tokenisation. This replaces a clinical trial participant's personal identifiable information with a unique, de-identified token, which enables the gathering of a participant's health data on an ongoing basis through secondary sources such as electronic health records. As a result, researchers can gather real-world data on the safety and effectiveness of drugs long after a trial has concluded, while being better able to track patients after their participation. Furthermore, this method allows deeper insights through the ability to analyse trends in disease and treatment patterns over time and reduces the dependence on unreliable patient recollection.

Cardiovascular outcome trials

Multiple studies have demonstrated improvements in long-term cardiovascular outcomes with the use of GLP-1 receptor agonists in patients with diabetes.[73] Based on these findings, some GLP-1 receptor agonists have label indications for secondary prevention in diabetic patients with established cardiovascular disease, and others are also indicated for primary prevention. Considering the reductions in cardiovascular events in obese patients treated with bariatric surgery, it is hypothesised that comparable weight loss reductions with GLP-1 and other incretin agonists could also improve cardiovascular health.

Recently, semaglutide has demonstrated a reduction in major adverse cardiovascular events in nondiabetic patients with obesity.[74] Semaglutide has also recently demonstrated symptomatic improvement in patients with obesity who also have heart failure and preserved ejection fraction.[75] Ongoing study is needed to establish whether hard clinical heart failure endpoints can also be reduced. Other incretin receptor agonists are under active study for the prevention of long-term cardiovascular events in patients with obesity. If positive, these results would further support the cost effectiveness of these pharmacologic interventions for weight loss.

Given the recent success of obesity therapies such as semaglutide, tirzepatide and retatrutide, what do you think the focus of future obesity therapies will be?



Base: All respondents (n=103)

Conclusion

As we look to the future of human health, the expected continued growth in the incidence of obesity is of high concern.[7] Prevention is one method for addressing this epidemic. However, while lifestyle interventions may lead to health benefits, the complexity of this problem requires a multipronged approach. Effective pharmacologic therapies are likely to play a critical role for many obesity patients. These advances in treatment have the potential to curb not only obesity, but also the multitude of associated co-morbidities.

Recent studies employing GLP-1 receptor agonists and other incretin mimetics have achieved unprecedented levels of weight loss rivalling that seen with bariatric surgery. Some agents have demonstrated reductions in cardiovascular events, while others are under active investigation for this purpose. New therapeutic agents are likely to further enhance pharmacotherapeutic options and benefits. Genomic studies have the potential to identify new molecular targets, given that the identification of naturally occurring protective alleles have translated into effective therapeutics in other cardiovascular diseases.[25]

There is growing interest in the simultaneous development of assets not just for diabetes and obesity, but also for pre-morbid conditions, such as prediabetes and steatosis (fatty liver), with potentially more public health impact but currently without approved regulatory registrational pathways. Given the broader range of potential patients suitable to study and the currently separate indications to be treated, ICON is exploring potential advantages to innovative uses of master protocols, which are constructed to test multiple hypotheses with an overarching set of procedures intended to improve efficiency. This maximises the ability to identify relevant populations at screening and to direct them to appropriate sub-studies.

Ultimately, the existing and future therapies must demonstrate cost effectiveness and need to be available to underserved populations globally. Efficient drug development strategies are needed to facilitate the achievement of these goals.

Contact us to learn how our integrated approach to obesity studies and cross-disciplinary therapeutic area expertise can flexibly support your clinical development programme.

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Further reading

Weblink

Cardiovascular Insights

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Case study

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Case study

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Diversity and inclusion in clinical trials

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Factsheet

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Learn how ICON, the global leader in hepatology and NASH clinical development, can help unlock your programme's full potential and bring life-changing treatments to patients faster.

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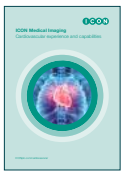
Factsheet



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