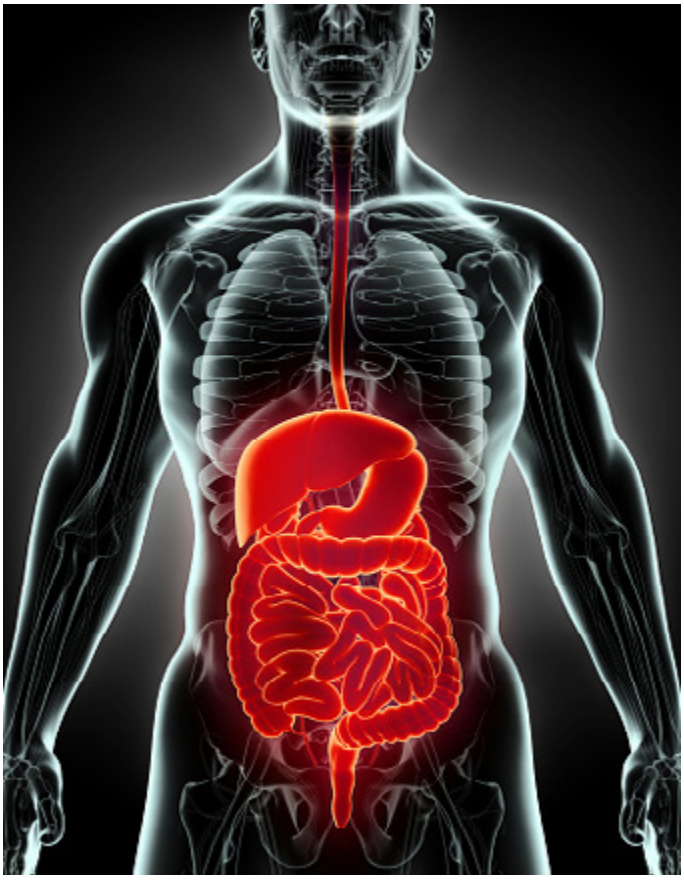
ALTASCIENCES

The Altascientist

ISSUE NO. 5

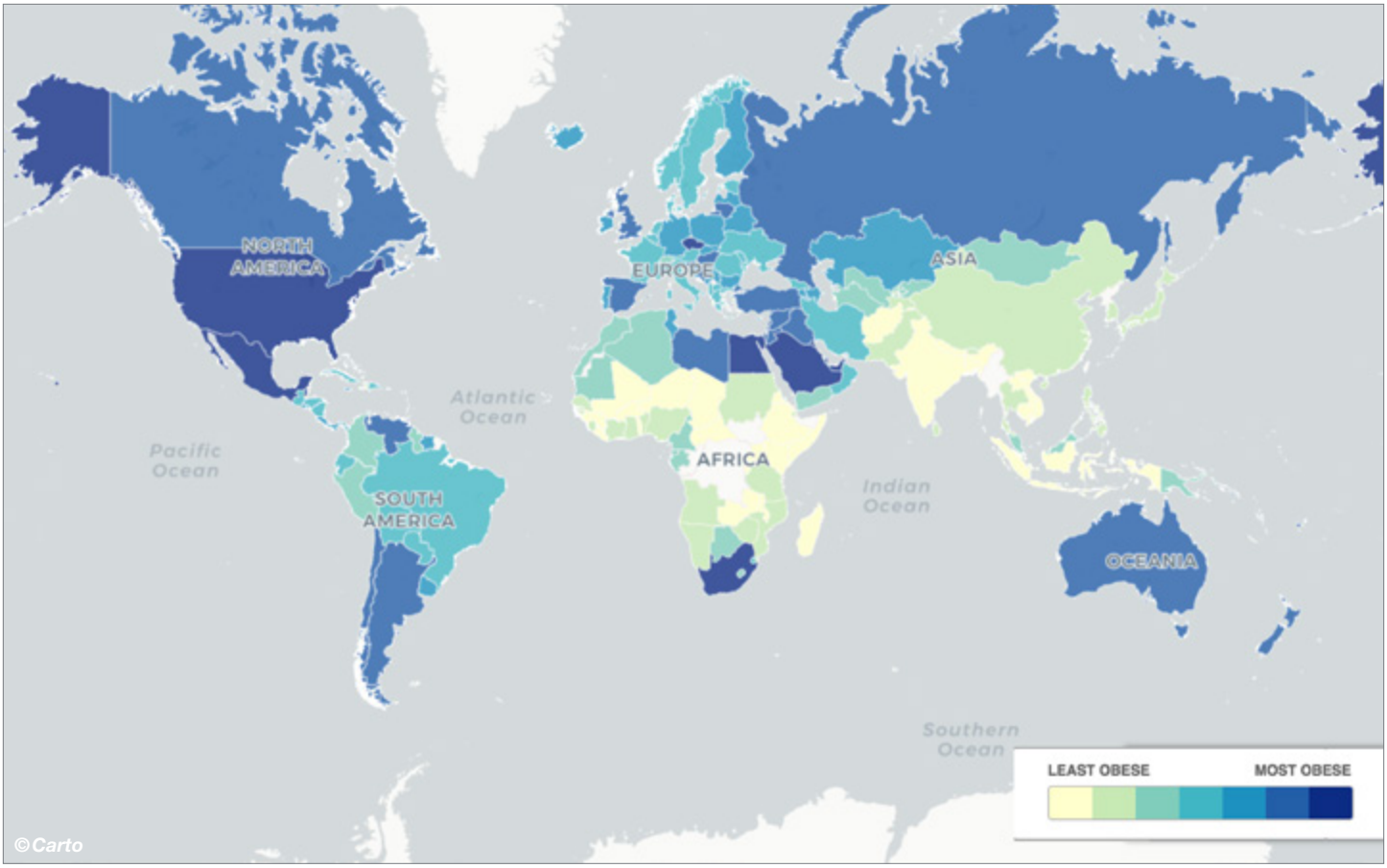
The Many Faces of Metabolic Disorders

Metabolic disorders are conditions that disrupt normal metabolism and the process of converting food to energy at the cellular level. They affect the ability of the cell to perform critical biochemical reactions that involve the processing or transport of proteins (amino acids), carbohydrates (sugars and starches), or lipids (fatty acids).



Metabolic disorders can take many forms, with obesity and diabetes being the most common. The worldwide prevalence of obesity has nearly tripled between 1975 and 2016. Once considered a high-income country problem, obesity is now on the rise even in low- and middle-income countries. Overall, about 13% of the world's adult population (11% of men and 15% of women) was considered obese in 2016. In that same year, it was estimated that 41 million children under the age of 5, and 340 million children and adolescents aged 5 to 19, were considered overweight or obese.

Scientific research in obesity focuses on learning more about the associations between dietary patterns and obesity development and its treatment. This includes the assessment of behavior, medications, devices, and



surgical approaches. According to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), clinical trials aim to identify which patients may respond to a specific drug or type of diet, how bacteria in a person's gastrointestinal tract may affect his or her risk of becoming obese, how metabolism influences obesity, how a mother's weight gain during pregnancy can affect her later health and the health of her baby, and how physical activity can improve a person's weight.

At Altasciences, we have over 45,000 obese or morbidly obese patients in our database, and have screened over 2,000 overweight or obese participants for clinical trials in the past 4 years, enrolling 1,000 in our studies thus far. Many of these studies require long confinement periods to ensure consistency in diet and exercise. We have conducted several studies exceeding 30 overnight stays, and have domiciled patients for as many as 66 overnights.

Our subject completion rate in obesity studies currently stands at an impressive 90%. This is achieved by our patient-centric approach, such as upscale facilities equipped with high-tech entertainment lounges (including Wi-Fi, bed-side touch-screen systems, gaming rooms, and internet café), kitchens that provide meals designed by dieticians with precise calories from fat, carbs, and protein, daily visits by an investigator (independent of the study requirements), concierges to look after patient needs, and on-site security. These are just some of the features that make Altasciences an obvious choice for sponsors seeking to conduct obesity studies, particularly those that require long confinement periods.

Metabolic Clinical Development Solutions

- Clinical Pharmacology Studies
- Proof-of-Concept Models
- Laboratory Services
- Patient Recruitment
- Investigator Site Recruitment
- Medical Imaging
- Expert Consultants

Ask the Expert

Ingrid Holmes
General Manager, Clinical Operations
Altasciences

Frequently Asked Questions on Clinical Trials for Metabolic Disorders

Can Altasciences recruit both type 1 and type 2 diabetics? Yes, we can recruit both type I and II diabetics. We have recruited as many as 75 patients in one study. The number we can recruit depends on the I/E criteria (e.g., BMI, A1c) and concomitant medications that are permitted.

How big is Altasciences' NAFLD/NASH patient database? We have diagnosed more than 50 of our participants as having phenotypic NASH, using a strict protocol-specific phenotype. Phenotypic models can vary from study to study. Depending on the model applied, our NASH database ranges from 50 to 150, and our modeled NAFLD database is >300. Phenotypic NASH is determined by BMI, A1c, ALT, and/or AST, although a true diagnosis requires a liver biopsy.

What types of glucose tolerance or insulin sensitivity models does Altasciences have experience with? We have performed oral glucose tolerance tests (OGTT) and mixed meal tolerance tests (MMTT) in healthy normal volunteers, obese patients, and diabetics. We have also performed glucose clamping studies in diabetics using YSI-2900 glucose analyzers.

Can Altasciences perform imaging in NASH?
Yes, we have access to a FibroScan®, a specialized ultrasound machine for liver. We also have multiple qualified imaging vendors, approved by central MRI readers, who perform MRIs that scan for liver fat density.

Does Altasciences have metabolic kitchens to provide meals with precise calories from fat, carbs, and protein? Yes, we use kitchens at our facilities or pre-qualified caterers to prepare precise diets provided by dieticians.

How many overweight or obese, but otherwise healthy, subjects has Altasciences recruited for studies over the years? We have screened more than 2,000 overweight or obese individuals with BMI values ranging from 30 to 60 in the past 4 years. Over 1,000 have enrolled in our clinical studies.

How long are the treatment and evaluation periods for the obesity studies conducted by Altasciences? The treatment and evaluation periods have ranged from 45 to 177 days. Our retention and completion rate for these subjects has been approximately 90%.

What types of studies has Altasciences conducted in populations suffering from metabolic syndrome, obesity, diabetes, and NASH? We have conducted many different types of studies in these patient populations, from first-in-human (FIH), single ascending dose (SAD) to proof-of-concept (POC) studies. The focus of the studies ranges from glucose tolerance to pharmacokinetics, comparing obese subjects to those with normal weights.

An Epidemic Still on the Rise

Several epidemiologic studies reveal a direct link between the escalation of obesity and diabetes. The pathophysiology connecting the two metabolic disorders is mainly attributed to two factors: insulin resistance and insulin deficiency. Research shows that if you are obese, your chances of developing type 2 diabetes are 80 times greater than a person whose body mass index (BMI) is within a normal range (under 25). Type 2 diabetes is a dysfunction in the way the body metabolizes glucose, causing it to rely on alternative energy sources from tissues, muscles, and organs. Individuals suffering from the disease are either resistant to insulin or do not produce enough of it to maintain healthy blood glucose levels. Type 2 diabetes makes up about 90% of cases of diabetes, with the remaining 10% comprised of type 1 diabetes mellitus (T1DM), and gestational diabetes. T1DM is an equally important form of diabetes, characterized as a chronic illness where the body in unable to produce insulin due to the autoimmune destruction of the beta cells in the pancreas.

Altasciences' ability to effectively recruit patients, our clinical operational experience, and robust list of validated bioanalytical assays, including Exenatide, Glucagon, Insulin Glargine, M1, M2, Insulin Aspart, and Metformin, provide the perfect solution for organizations developing treatments for metabolic disorders such as diabetes.

We recently partnered with a specialty pharmaceutical company leveraging its novel formulation technology platforms to develop and commercialize ready-to-use, liquid-stable injectables, on a randomized, controlled, single blind, two-way crossover study to evaluate the efficacy and safety of their investigational glucagon injection in T1DM subjects in a state of insulin-induced hypoglycemia following baseline euglycemic steady-state.

Altasciences' Supporting Case Study

A Multi-Centre, Randomized, Controlled, Single-Blind, 2-Way Crossover Study to Compare 2 Glucagon Formulations for Induced Hypoglycemia Rescue in Adults with Type 1 Diabetes

Study Overview

This study was a non-inferiority, multi-centered, randomized, controlled, single-blind, two-way crossover, inpatient study in subjects with T1DM. The primary objective was to demonstrate the efficacy of a glucagon injectable device when compared to an existing treatment in treating insulin-induced hypoglycemia. Up to 85 male and female subjects diagnosed with T1DM were randomized to the investigational product or comparator in a crossover fashion over 2 periods. Altasciences participated in this multi-center trial and was able to recruit and randomize 8 patients in a two-week period despite the restrictive inclusion and exclusion criteria and the need to qualify by demonstrating a capacity to maintain stable glucose levels. Subjects were admitted the evening prior to check-in for continuous glucose monitoring and to begin fasting. Eligible subjects were evaluated for their capacity to maintain plasma glucose levels within a pre-specified range for at least 30 minutes when given a stable infusion of insulin. These subjects then continued to the insulin-induced hypoglycemia phase of the study that was performed through a monitored, standardized induction protocol. Once a stable state of hypoglycemia was reached, subjects were administered a subcutaneous injection of either the investigational product or comparator product. Glucose monitoring continued for 3 hours post-dose and subjects were discharged once medically stable and glucose levels returned to normal. After a pre-defined washout period, subjects returned to the clinic and the study procedures were repeated as each subject crossed over to the other treatment. Subjects were evaluated for hypoglycemia symptoms, injection site discomfort and reactions, and other measures of safety and tolerability.

Study Details

- Class of Drug: Anti-hypoglycemic agent
- Indication: Type 1 diabetes mellitus
- Population Type: Type 1 diabetes mellitus
- Number of Participants: 85 across multiple sites
- Time to recruit panel at Altasciences: 2 weeks for 8 patients (FSFV-LSFV)
- Study Design: Multi-center, randomized, single-blind, 2-way crossover
- Key Inclusion Criteria:
  - Males and females 18 to 75 years old diagnosed with type 1 diabetes mellitus for at least 24 months
  - Current usage of daily insulin treatment that included having an assigned "correction factor" for managing hyperglycemia
  - Random serum C-peptide concentration < 0.5 ng/mL
- Key Exclusion Criteria:
  - Pregnant or breastfeeding
  - HbA1c greater than 9.0% at screening
  - BMI greater than 40 kg/m^2
  - Renal or hepatic insufficiency
  - Hematocrit of less than or equal to 30%
  - BP readings at screening where SBP is less than 90 or greater than 150 mm Hg, and DBP is less than 50 or greater than 100 mm Hg
  - Clinically significant ECG abnormalities
  - Use of more than 2.0 U/kg total insulin dose per day
  - Congestive heart failure
  - Active malignancy within 5 years from screening
  - Current seizure disorder (other than with suspect or documented hypoglycemia)
  - Current bleeding disorder, treatment with warfarin, or platelet count below 50 x 10e9/L

Services Provided

Recruitment and clinical conduct.

Study Purpose

To demonstrate the non-inferiority of the investigational product versus the comparator with respect to efficacy as measured by a return to plasma glucose greater than 70.0 mg/dL in T1DM subjects in a state of insulin-induced hypoglycemia.

Methods

The key assessments used in this study were:

- Continuous glucose monitoring (via Dexcom G4)
- Euglycemic steady state maintenance
- Insulin-induced hypoglycemia via insulin infusion, and bedside glucose readings via Yellow Strings Instruments' (YSI) glucose analyzer
- Safety and tolerability assessments related to injection site reactions and hypoglycemia

Challenges and Solutions

Time constraints to complete study enrollment were tight. To overcome the challenge, we proactively used our internal database of over 750 type 1 diabetic patients weeks in advance to quickly enroll and dose 8 patients in 2 weeks (from IRB approval). Recruitment was executed mainly through targeted patient reach-outs, with little study-specific advertising. The flexibility of our recruitment strategies and robustness of our diabetic patient database proved to be key factors in meeting enrollment milestones and achieving a 100% completion rate.

Altasciences was the only clinical facility able to complete validation and use the state-of-the-art YSI 2900 Biochemistry analyzer for confirmatory bedside glucose measurements during the insulin-induced hypoglycemia procedure. This device accommodates 96-well formats and can support high throughput measurements of a range of chemistries, including glucose, lactate, glutamate, and ethanol. During the course of this study, it helped ensure safety during hypoglycemic induction by measuring glucose levels in real-time during insulin dosing.

A Hidden Threat: Nonalcoholic Fatty Liver Disease (NAFLD)

Much like obesity and diabetes, nonalcoholic fatty liver disease (NAFLD) is a global epidemic, with prevalence rates around 25% to 30%. NAFLD can be divided into the milder form, nonalcoholic fatty liver (NAFL) and the more aggressive form, nonalcoholic steatohepatitis (NASH). It is characterized by different levels of hepatic steatosis (fat deposition), inflammation (in NASH), and fibrosis. Hepatic steatosis can be seen either by imaging or histology.

For a NAFLD diagnosis, it is important to establish a lack of secondary causes of hepatic fat accumulation, such as significant alcohol consumption, long-term use of a steatogenic medication, or monogenic hereditary disorders. NAFLD, and specifically NASH, can lead to cirrhosis, which can eventually progress to portal hypertension and hepatocellular carcinoma (HCC). HCC is currently the fastest growing cancer type in the U.S. with the incidence of NAFLD-related HCC increasing at a 9% annual rate.

The traditional risk factors for NAFLD include age, sex, and central obesity. There is a very high prevalence of NAFLD in individuals with type 2 diabetes mellitus. In fact, some studies have suggested that approximately 30 to 60% of diabetic patients have NAFLD. It has a reported prevalence of 9.6% among diabetic adolescents and preadolescents, and 34% in patients aged 30 to 65 years. Cancer and liver-related mortality are the most common causes of death among patients with NAFLD/NASH. Currently the third leading cause for liver transplant, NASH is predicted to overtake hepatitis and rise to number one in the U.S. by 2030, as more hepatitis C virus (HCV) patients are treated with highly curative antiviral regimens.

In most patients undergoing evaluation, radiologic and laboratory findings are sufficient to make the diagnosis of NAFLD; however, liver biopsy is the standard and most accurate way to diagnose NASH. Biopsies are invasive and expensive, and are subject to sampling errors. Patients can be reluctant to comply because of risks of pain and severe complications. All these challenges have increased the motivation to find and apply noninvasive methods to diagnose the different stages of NAFLD.

Despite the growing prevalence of NAFLD/NASH, treatment options remain extremely limited. A large number of pharmaceutical companies have started to conduct clinical studies to develop treatments for NASH, but recruiting patients for these types of studies is very challenging as this disease does not present with clear symptoms and the majority of patients do not know they have it or are not diagnosed until significant damage to the liver has occurred. Even with the many therapeutic agents studied for the treatment of NASH, there are currently no FDA-approved drug therapies available for this disease.

> “One of our ultimate goals is to develop approaches for better diagnosis and management of chronic liver disease, which is currently an increasing worldwide concern, and demands early phase trials that require specific imaging and biomarker services. We are continuously expanding Altasciences’ therapeutic offerings in gastrointestinal disease-specific studies, particularly those intended to investigate the efficacy of drugs in patients with NASH.”

Dr. Gaetano Morelli
Medical Advisor, Altasciences

Altasciences' End-To-End Patient Recruitment Process and Patient Access for Nash Studies

An important reason why pharmaceutical companies want to partner with Altasciences is our particular expertise in recruiting patients for early-phase clinical pharmacology studies. We have completed over 50 early-stage trials involving antidiabetic and hypoglycemic agents, including insulin, GLP-1, SGLT-2, and DPP-4. Our database of over 225,000 participants allows us to recruit healthy participants very quickly, such as the 200 participants we enrolled in one day for a recent study.

More specifically, our vast searchable database includes:

- 20,000+ Metabolic Syndrome patients
- 35,000+ Obese patients (BMI >30)
- 10,000+ Morbidly obese (BMI >40)
- 250+ Nonalcoholic Steatohepatitis (NASH)
- 750+ Type I diabetics
- 1,500+ Type II diabetics

At Altasciences, we saw the developing need for patients with NASH and proactively built a database of patients suffering from the disease using an IRB-approved protocol we sponsored ourselves. Since NASH patients are often underdiagnosed, we knew we could not simply advertise for NASH. Instead, we worked with Dr. Morelli, one of our investigators, a gastroenterologist and an expert in NASH, to build a campaign based on a set of criteria the patients will recognize as applicable to them.

From our internal database, we selected patients who were obese or diabetic and identified those with a hemoglobin A1c value of over 6.5%, as values above 6.5% are linked with NASH. Our advertising campaign, targeted to these individuals, focused on obesity and diabetes, and was active for four months. In that time, we fielded over 400 calls, screened 200 patients and diagnosed 50 with phenotypic NASH, using BMI, gender, ALT and A1c values. Although a biopsy is the definitive diagnostic for confirming NASH, phenotypic NASH has been shown to correlate 80% to 90% with biopsy-confirmed NASH. Via this proactive campaign, we successfully began to build our NASH patient database.

Soon thereafter, a sponsor approached us to conduct a clinical study requiring NASH patients. The patients needed for the study were phenotypic NASH, and due to the mechanism of the study drug, the criteria were more selective than those used in prescreening. Additionally, the patients were required to have an MRI assessment of the liver. We knew these criteria would likely result in a greater screen failure rate than we had seen in our proactive screening, however our feasibility assessment assured us we could still succeed.

From February to May 2018, we conducted the study-specific recruitment campaign. We were one of 10 global sites recruiting, with many of the sites, including the U.S., having started several months earlier. As expected, the screen fail rate, even with the NASH patients in our database, was high at approximately 80 to 90%. Nevertheless, our recruitment was extremely successful and we became the top enrolling site within two months. When the overall objective was reached and recruitment was stopped, we had recruited more than 30% of the study patients.

We believe what truly sets us apart from the competition in the case of this NASH study, and all the other studies we conduct for our clients, is the end-to-end recruitment process we have at Altasciences.

Recruitment of healthy participants and patients is most successful when they have trust in the clinical research site. Feedback from patient focus groups confirms that word-of-mouth referral is the most common reason a person decides to participate in a study at Altasciences. In order to retain this level of trust and confidence, we go to great lengths to ensure the experience of participants at any of our three sites (Kansas, Fargo, Montreal) is always a positive one. Our well-trained staff ensures not only participant safety, but their overall satisfaction with their experience. Our comfortable clinics have ample entertainment and, most importantly these days, stable, fast internet. We provide quality meals and snacks, with as much menu variety as the study protocol allows.

We implemented the Lean 6 Sigma process to streamline all our procedures and reduce patients' unnecessary wait times, including during screening and return visits. There are 'Happy or Not' Smiley Terminals™ throughout our clinics to capture and analyze feedback in real time and make measurable improvements, and we conduct regular satisfaction surveys with our participants. All of these patient-centric elements add up to a consistently positive experience for our study participants, who then encourage others to participate in our studies.

The backbone of our recruitment process is a robust Customer Relationship Management system, which we like to call a Participant Management System (PRM). With the PRM, we can extract participant data, and communicate efficiently and effectively with specific segments as needed. With a few clicks of a mouse, we can reach out to a targeted list of participants within our database, using automated e-mail communications, throughout a study's progress.

A crucial benefit offered by our PRM is the ability to target and manage different types of web-based contacts, and track their progress. Using various online tools, we may publish banner ads reaching healthy males under 35, located within 50 miles of one of our facilities; or send an e-mail of our newsletter to a certain demographic identified as diabetic in our database. We can take it one step further and reach out to those same diabetics (if they haven't responded to the e-mail), and run a Facebook banner campaign that will only appear to them.

With reports from our PRM, social media platforms, and Google Analytics, we can better measure the success of our interactions in real-time. This allows us to react and adjust our targeted audience or message. In addition, we can accurately see the multiple touch points in the funnel leading to a participant being dosed on study.

Our online Participant Portal is unique in the industry. Returning participants access the portal to schedule themselves in a study. They can schedule a screening appointment for studies that match their profile, track screening results, and confirm their presence for the start of a trial. Automated reminders are sent throughout the process, ensuring participant attendance along the way.

This end-to-end, patient-centric recruitment process, which begins long before we have a confirmed study, has enabled Altasciences to have similar success across a large number of patient populations, including diabetes, substance abuse, Hepatitis B & C, rheumatoid and osteoarthritis, and functional ileostomy. All the steps in the process add up to exceed our sponsors' expectations in patient recruitment.

References

Al-Goblan, A. S., Al-Alfi, M. A., Khan, M. Z. (2014). Mechanism linking diabetes mellitus and obesity. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy; Vol. 7: 587–591.*

Chalasani,N., Younossi Z., Lavine J. E., Charlton M., Cusi K., Brunt M., Sanyal, A. J. (2018). The Diagnosis and Management of Nonalcoholic Fatty Liver Disease: Practice Guidance From the American Association for the Study of Liver Diseases. *Hepatology, Vol. 67, No. 1.*

Diabetes Care Community. The Link Between Obesity and Diabetes. (2018). Available: https://www.diabetescarecommunity.ca/diabetes-overview-articles/link-obesity-diabetes/?gclid=EAIaIQobChMInPyF4MKN3QIVRNbACh3r5gXGEAAYASAAEgKa_fD_BwE

Grandison G. A., MD, Angulo, P., MD. (2012). Can NASH Be Diagnosed, Graded and Staged Noninvasively? *Clin Liver Dis.; 16(3): 567–585.*

John Vizuete. J., Camero, A., Malakouti, M., Garapati, K., Gutierrez, J. (2017). Perspectives on Nonalcoholic Fatty Liver Disease: An Overview of Present and Future Therapies. *Journal of Clinical and Translational Hepatology; Vol. 5: 67–75.*

National Institute of Diabetes and Digestive and Kidney Diseases. Clinical Trials for Overweight & Obesity. (2018). Available: https://www.niddk.nih.gov/health-information/weight-management/adult-overweight-obesity/clinical-trials

Perumpail, B. J., Khan, M. A., Yoo, E. R., Cholankeril, G., Kim, D., Ahmed, A. (2017). Clinical epidemiology and disease burden of nonalcoholic fatty liver disease. *World J Gastroenterol. 2017 Dec 21; 23(47): 8263–8276.*

Renew Bariatrics. Report: Obesity Rates By Country – 2017. (2017). Available: https://renewbariatrics.com/obesity-rank-by-countries

Singh, S., Kuftinec, G. N., Sarkar, S. (2017). Non-alcoholic Fatty Liver Disease in South Asians: A Review of the Literature. *Journal of Clinical and Translational Hepatology; Vol. 5: 76–81.*

Smith, O. (2017). World Obesity Day: Which countries have the biggest weight problem? Available: https://www.telegraph.co.uk/travel/maps-and-graphics/the-most-obese-fattest-countries-in-the-world

Verma, S., Hussain, M. E. (2017). Obesity and diabetes: An update. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews; Vol. 11, Issue 1: 73-79*

World Health Organization. Obesity and Overweight. (2018). Available: http://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight

About Altasciences

Altasciences is a forward-thinking, mid-size contract research organization offering pharmaceutical and biotechnology companies of all sizes a proven, flexible approach to preclinical and early phase clinical studies, from lead candidate selection to proof of concept. For over 25 years, Altasciences has been integrating into clients' projects to help support educated, faster, and more complete early drug development decisions. Altasciences' full-service solutions include preclinical safety testing, clinical pharmacology, bioanalysis, program management, medical writing, biostatistics, data management and more, all of which can be tailored to specific sponsor requirements.

Altasciences… helping sponsors get better drugs to the people who need them, faster.

Authored by: Taline Chichekian