Metabolic Syndrome (also referred to as Insulin Resistance Syndrome, Syndrome X, and the Deadly Quartet) is diagnosed by several combined risk factors, and is most notably defined by its patients’ pro-inflammatory state. Metabolic syndrome identifies a cluster of symptoms affecting multiple organs and systems, most importantly the cardiovascular and sugar metabolism systems. Frequent symptoms include abdominal obesity, elevated blood pressure, and insulin resistance; however, according to the American Heart Association, there are no well-accepted criteria for diagnosing the syndrome.

According to NHANES (National Health and Nutrition Examination Survey) data, 30% of North American Adults may have Metabolic Syndrome. This is significant since it has been established as a key indicating factor for a patient’s likelihood of future diagnosis for serious illnesses (including diabetes and coronary heart disease). This risk increases with age, particularly in patients over age 60. Further, researchers have identified Metabolic Syndrome patients as being at double the risk for Myocardial Infarction (MI), Heart Disease, or Stroke, and at 5x greater risk for Diabetes. This syndrome is so far-reaching that Metabolic Syndrome, Related Disorders, and Other Predisposing Factors now include: Non-alcoholic SteatoHepatitis (NASH); Polycystic Ovarian Syndrome (PCOS); Obstructive Sleep Apnea; Cholesterol Gallstones; Gout; and even HIV-Protease Inhibitor Therapy.

The most common Metabolic Syndrome symptoms (or disease indicators) include abdominal obesity (called central adiposity and visceral adiposity); insulin resistance in muscle; and fatty liver hepatitis. Serious metabolic problems result from these issues as the extra adipose tissue produces adipokines and harmfully elevated levels of TNF-alfa and IL6 (pro-inflammatory cytokines), Hs-CRP adiponectin, Serum Amyloid A, Leptin, and MCP-1. As adipose tissue increases in the body, the presence of macrophages also increases, producing pro-inflammatory cyto-1 chemokines. Concurrently, levels of protective IL-10 decrease. Further Metabolic Syndrome symptom presentations include increased hyperinsulinemia, hypertension, hyperglycemia, high triglycerides, and lowered levels of health-preserving LDL.

Obesity, particularly located in the abdominal area, is associated with insulin resistance to peripheral glucose and fatty acid utilization (which often leads to type 2 diabetes mellitus). The associated elevated glucose levels, increased insulin blood levels, and adipokines may also lead to vascular endothelial dysfunction, disturbance in lipid profile, hypertension, and vascular inflammation. Further, these risks will likely stimulate the development of cardiovascular disease.

Various predictive diagnostic indicators have been identified in Metabolic Syndrome cases, including measures of non-HDL Cholesterol as a biomarker predictor of cardiovascular events; Apolipoprotein B indicating the total atherogenic particle number circulating in a patient’s system; and MicroAlbunuria (urine albumin levels). Tracking these indicators has successfully predicted poor patient outcomes in 5-year follow-ups.

Because metabolic syndrome is not a single disease, monitoring patient outcomes to a therapeutic regimen must take into account a complex cluster of factors and biomarkers. Researchers (like Dr. Ishwarlal Jialal, of University of CA, Davis Medical Center) explain that the biggest challenges in conducting a metabolic syndrome trial include 1) finding the patient population, 2) choosing the right endpoints or biomarkers, and 3) defining the inclusion/exclusion criteria for a useful study. Designing clinical trials that accurately predict patient outcomes is therefore more complex than designing trials that monitor outcomes for a disease.

**Clinical Trial Design**

To meet the increasing need for pharmacotherapies to treat Metabolic Syndrome, SGS’s Clinical Trials optimization processes have created tools for organizations to better identify, treat, and
monitor patients and test their emerging therapies. SGS specializes in how to conduct and improve Therapeutic Clinical Trials, focusing on improving processes and study development. Recent work has honed several study designs for research efforts in order to identify the most appropriate design and biomarkers for Metabolic Syndrome Patients, and then track the effects of tested therapeutic compounds in proof of concept studies.

Different approaches are recommended to optimize the study depending on the specific trial objectives. Combined protocols run in a sequential or parallel manner are highly recommended in order to accelerate the study progress. This streamlined design reduces cost and time. In this scenario, in addition to the First-In-Man (FIM) trial, it is possible to add to the same protocol the Single Ascending Dose (SAD), Multiple Ascending Dose (MAD), Food Effect (FE) and the Proof-of-Concept (POC) trials. This combined protocol design requires just one submission to the health authorities and ethics committee. It’s important to know that in France submitting results from one part of the combined protocol while awaiting the green light from authorities before starting the next part is not required; so the combined protocol time savings is substantial. In order to gain the full efficiency of running a combined protocol trial, it is important to keep the number of amendments down to a minimum. This can be accomplished with experience and understanding of how to appropriately design and word the protocol from the very beginning. It is also critical to remember that the safety and tolerability data are always the main study objectives. In dealing with a Metabolic Syndrome clinical trial, a key planning consideration is which population to use as study subjects: healthy volunteers or patients. Both populations present advantages and disadvantages. Using healthy volunteers during the SAD, MAD and FE portions will accelerate the study progress and reduce the recruitment issues. In this scenario, the final step consists of the POC in a target patient population with long term treatment as the main component. Alternatively, by using patients for every part of the combined protocol, the recruitment challenges are increased. The primary reason for the increased challenge is that the target patient population has to be clearly defined with inclusion / exclusion criteria (including: Abnormal laboratory tests, Abnormal ECG and Blood Pressure results and whether or not the patients are currently receiving treatment). Whatever scenario is used, the appropriate biomarkers must be chosen to measure as endpoints in order to verify if a drug candidate has a positive or negative result. Lastly, there is no one-size-fits-all study design. By utilizing an experienced team, each study can be thoughtfully adapted for the chosen population and goals in order to have the most effective data.

It is important to clearly identify the endpoints in the design of the protocol in order to have data about the efficacy of the compound as early as possible during the clinical trial process. These endpoints often involve data on biomarkers. The selected biomarkers should be sampled frequently during the clinical study in the patient population. The subject verification process will be more efficient by testing for specific biomarkers throughout the clinical process, including during the definition period for subject selection criteria, disease status, and treatment identification. By collecting biomarker data throughout the trial, during FIM, MAD, and particularly MAD trials, efficacy data can even be obtained leading up to the POC trial. Since patients with Metabolic Syndrome frequently require long-term care, this can also be provided as ambulatory care in order to perform additional assessments without requiring admission to the hospital or unit. This additional long-term data can provide the sponsor with more information on the study drug safety profile.

In addition to understanding how combining study protocols may streamline the clinical trial process, one must also identify and proactively address the other challenges of setting up a Metabolic Syndrome clinical trial very early in the process. For example, to address recruitment and capacity (for healthy and target patients), one should consider using a strong and secure internal database and routine follow-up with volunteers (ideally, working within a hospital network). Also, consider involving a Key Opinion Leader very early on to help advise on setting the initial study guidelines, to provide guidance on participant inclusion / exclusion criteria and for biomarker selection. Important patient inclusion / exclusion criteria to consider are statin usage, concomitant meds (for hypertension and diabetes), lab and ECG tests, sex, ethnicity, and smoking status. Inclusion of diverse patients (including healthy subjects) in the FIM study is additionally beneficial.

In summary, to streamline metabolic syndrome trial study processes, SGS advises performing initial POC trials as soon as possible directly in the target population and using a clear, pre-established decision tree for protocols to proceed in a timely manner. When possible, implement a combined protocol, with clearly-defined and traceable biomarkers and endpoints, to benefit from the time savings. Due to the complex “special population” targeted, special attention should be paid to subject recruitment as this is crucial to ensure the clinical trial success. Finally, build up an experienced project team.

ABOUT SGS

SGS Life Science Services offers a complete package of integrated services from lab analysis and FIM to Patients trials. Recognized for its expertise and experience in complex early phase trials (such as FIM, Combined protocols, POC, and 14C ADME trials), we are Early Clinical Development Specialists with 35 years of experience in clinical pharmacology. SGS has large capacities to deliver, including 2 Phase I units in France and Belgium; a large Subject database of 16,500 volunteers; and Bioanalytical labs featuring mass spectrometry, biomarkers and immunogenicity.

With innovative study designs, optimal facilities and strong regulatory intelligence, SGS can favorably impact client’s drug development timelines and decision-making process.
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