Centralised ECGs Help Ensure Cardiac Safety of Obesity Drugs

Abstract

Obesity rates have dramatically increased over the past 20 years, making it one of the most prevalent health problems in the world. Despite this, there are only a very small number of adequately safe and effective obesity drugs available on the market to treat the condition. Many potential weight-loss drugs have either failed to progress through drug development processes or have been denied approval by regulatory agencies. In addition, many have been withdrawn from the market, having been associated with dangerous cardiovascular events. Due to this, the FDA Endocrinology and Metabolic Drugs Advisory Committee has recently introduced recommendations for drug manufacturers, requiring the submission of Phase II or III clinical trial data demonstrating the absence of cardiovascular risks of new obesity drugs. Centralised ECG trials have emerged as a viable method for helping drug companies provide reliable cardiovascular data in their attempts to achieve regulatory compliance, while also benefiting from significantly improved data accuracy and reliability, time and cost savings, and access to breakthrough technologies.

The Obesity Epidemic

The latest statistics from the NHS Information Centre for Health and Social Care show that over a quarter of UK adults are classified as obese (26% of both men and women aged 16 and over).[1] In America this figure is even higher, with one-third of US adults classified as obese.[2] In the NHS study, when waist circumference and BMI were used to assess risk of health problems, 22% of men were estimated to be at increased risk; 12% at high risk and 23% at very high risk in 2010.

Obesity is a dangerous condition, which substantially increases the risk of morbidity from hypertension, dyslipidemia, type 2 diabetes, coronary heart disease, stroke, gallbladder disease, osteoarthritis, sleep apnea and respiratory problems, as well as endometrial, breast, prostate and colon cancers.[3] In addition to the high health burden, obesity is also associated with increased medical costs. In a speech given by David Cameron in 2011, it was reported that obesity costs the NHS £4 billion a year, and within four years this number is expected to rise to £6.3 billion.[4]

Safety Issues with Weight-Loss Drugs

Until this year, there have been no satisfactorily safe and effective obesity drugs commercially available on the market. Many potential weight-loss drugs have either failed or been abandoned by drug development companies and there have been several obesity drugs withdrawn from the market due to safety concerns and adverse side-effects. In 1997, two popular anti-obesity drugs, Fen Phen and Redux, were pulled from the market by the US Food and Drug Administration (FDA) because of potentially life-threatening heart valve damage.[5] Additionally, in 2010, the obesity drug Meridia was recalled for causing an increased risk of stroke and heart attack in populations already prone to these dangerous cardiovascular events.[6]

The past few months have seen the approval of two new obesity drugs, the first approvals for drugs of this nature in 13 years. Lorcaserin and Qsymia (formally known as Qnexa) have both been approved by the US FDA recently; however, stringent measures are being put in place to ensure their safety, with them both requiring to undergo a number of post-marketing studies, including a long-term cardiovascular outcomes trial. These therapies are now seeking regulatory approval in additional territories. Another obesity drug, Contrave, is currently seeking regulatory approval again, after being previously rejected by US regulators over safety concerns. A huge opportunity is presented for pharmaceutical sponsors to make a significant impact on the lives of obese people with long-term drug therapy. However, there have been several challenges, mounting concerns and an increasing number of hurdles required to continue development programmes and ultimately gain regulatory approval for any new weight-loss drugs.

In general, weight loss has been tied to positive effects on the heart, but the few trials conducted on the long-term heart safety of obesity drugs have shown that these drugs either increase heart risks, or have little to no effect on heart health. As a result, the FDA will no longer approve a drug for the masses based on a small treatment benefit and without evidence of future improvement on patient health. In clinical trials, Contrave raised pulse rates and blood pressure slightly, a warning sign that the drug might increase the risk of heart attacks, strokes or other cardiovascular problems. As a consequence, in order to gain regulatory approval, the FDA has informed the drug maker that a cardiac safety study must be first conducted to prove that Contrave does not increase the risk of adverse cardiovascular events.[7]

Regulatory Requirements

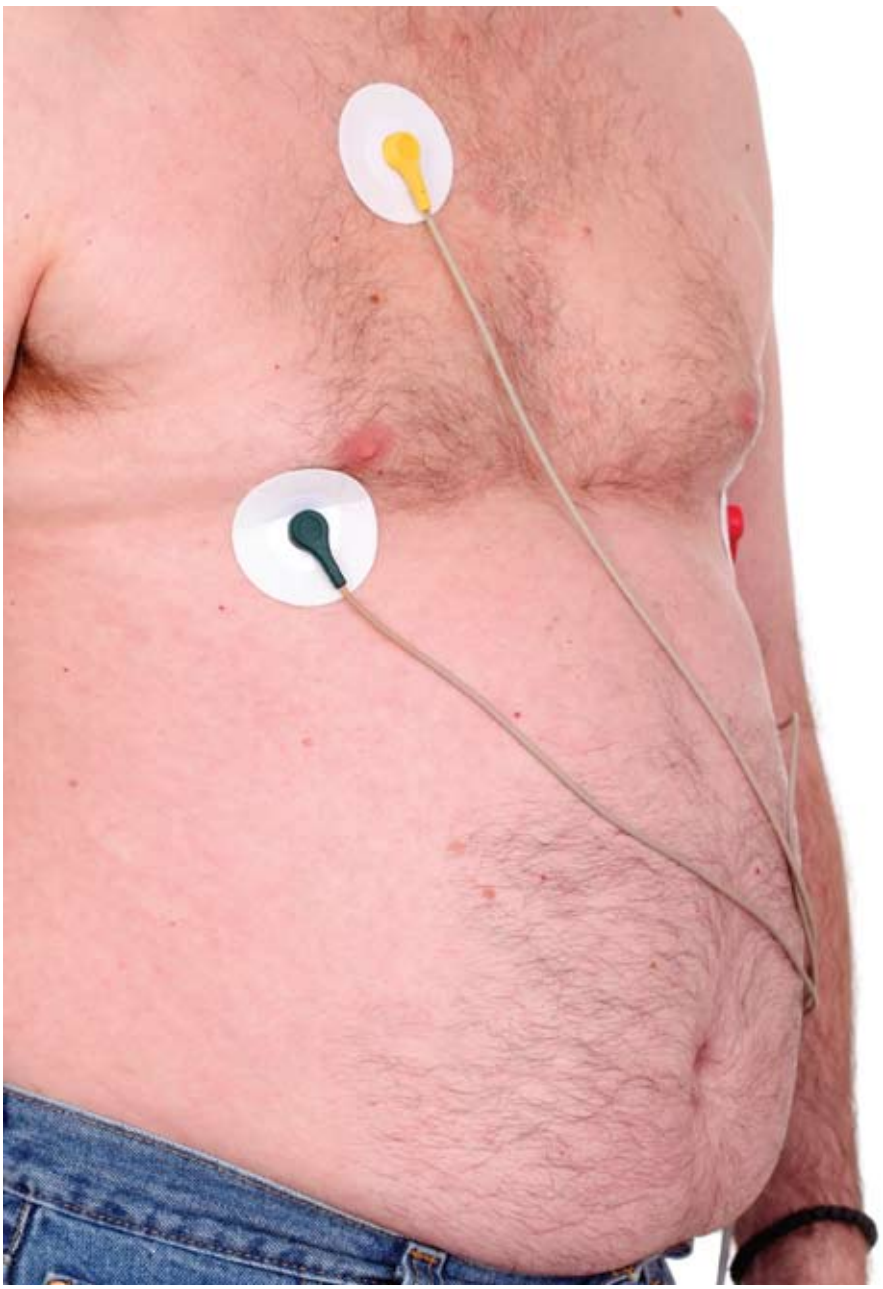
On March 29, 2012, after gaining information from experts in obesity, diabetes, cardiology and statistics, the FDA Endocrinology and Metabolic Drugs Advisory Committee recommended that drug companies be required to submit Phase II or III clinical trial data to prove absence of cardiovascular risks for new obesity drugs, even if clinical trials do not initially show evidence of precipitating cardiovascular events.

According to the recommendations, obesity trials should randomise approximately

3000 subjects to the active drug and at least 1500 subjects to a placebo for one year of treatment. The FDA requires that patients in Phase III obesity drug trials have a body-mass index (BMI) of at least 30 (or 27 plus comorbidities). The drug should demonstrate either mean efficacy (a >5% difference in weight loss between treatment and placebo) or categorical efficacy (at least 35% of treated patients lose >5% of their baseline body weight, approximately double the proportion in the placebo group).[8]

In addition to these already established requirements to prove efficacy, almost all committee members agreed that the major adverse cardiac event (MACE) data should come from either cardiovascular-outcome trials or meta-analyses. Additionally, 17 to 6 voted in favour of the new suggested requirements.[9]

Centralised ECG trials can help drug manufacturers comply with the new stringent regulatory requirements, while also enjoying other significant benefits, including dramatically improved data quality and accuracy, time and cost savings, access to cutting-edge technologies and improved overall efficiency of processes.



Cost and Time Savings

To date, many drug companies have been reluctant to use centralised ECGs due to the common misconception that such an approach is more expensive than a localised or internal model of data collection, primarily as a consequence of the hardware distribution involved. When adopting a decentralised model, the majority of collection, transcription, cleaning and interpretation of ECG data is conducted by the pharmaceutical company and the particular monitoring site. As a consequence, there is a belief that a core laboratory that forms part of a centralised system is a non-essential additional expense.

However, a centralised approach is often proven to be more cost-efficient. A decentralised model requires companies to pay a substantial ECG acquisition fee, which includes charges for technician time and the use of ECG machines at each investigator site. When using a centralised approach, this fee is reduced since all work is performed in a singe core laboratory. In addition, a decentralised method involves manual transcription, monitoring and quality control of data from multiple sites, increasing labour costs, and data entry errors. Additional cost savings are achieved since a centralised approach dramatically reduces the reconciliation of discrepancies and queries due to inconsistent interpretation during the statistical analysis and medical review phase.

In addition, through implementation of a centralised model, pharmaceutical companies can significantly accelerate analysis time since the collection, transcription, cleaning and interpretation of ECG data are performed using standardised procedures in a singe core laboratory. Here, there is a higher probability to detect cardiac risks earlier in the drug development process, as a result, minimising wasted time and cost expenditure planning for a new drug compound that is not viable.

Improved Data Quality and Accuracy

When a decentralised model is employed, ECG studies are

conducted across many different investigator sites, using local ECG instrumentation. However, different types of instruments use varying algorithms for calculations, while local investigators or their contracted specialists employ various interpretation guidelines and methods. As a consequence, inconsistent results often occur, presenting a considerable challenge for drug manufacturers, who require accurate and reliable data in order to confidently assess the cardiac safety of compounds in clinical trials.

On the contrary, a centralised approach eliminates inconsistencies by facilitating digital collection of high quality data in a standardised format with the use of consistent and validated systems. Qualified individuals assess all interval duration measurements (IDMs), and qualified cardiologists evaluate all ECG data. These cardiologists are trained to follow standardised procedures which are continually validated through a quality control programme. As a result of these standardised processes, companies benefit from much cleaner and more accurate data.

Access to Breakthrough Technology

In order to gain and maintain a competitive advantage, pharmaceutical companies must continually invest in new, ground-breaking technologies. This is enabled through the adoption of a centralised method, which involves the use of innovative technological solutions, such as lightweight and compact ECG instrumentation. New ECG machines have a significantly smaller footprint and are lighter than their predecessors, thereby removing the challenges raised by the deployment of traditional heavy and expensive instrumentation. Innovative new ECG devices are much easier to manoeuvre and are less costly to ship and store. Due to their compact size, the instruments also offer an improved service on a technical level, enabling more consistency and improved accuracy while effortlessly integrating with computer systems through a simple web application.

Conclusion

According to statistics from the NHS Information Centre for Health and Social Care, obesity has more than doubled over the past 20 years in Australia and New Zealand, and increased by half in the United Kingdom and United States. Obesity rates in many Western European countries have also increased substantially over the past decade, making this a global concern. This is an extremely alarming situation since obesity has long been associated with life-threatening health conditions, including cardiovascular diseases. On top of that, many potential weight-loss drugs have been found to also cause dangerous cardiovascular events. To address this problem, the FDA Endocrinology and Metabolic Drugs Advisory Committee recommends that pharmaceutical manufacturers should submit Phase II or III clinical trial data demonstrating the cardiac safety of new obesity drugs. Centralised ECG data collection, monitoring and analysis performed in a single core laboratory facilitates regulatory compliance, while also allowing for improved data accuracy and reliability, time and cost savings, and access to innovative technologies.

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