Cutting Edge ECG Technology Reinforces the Continued Advancement of Centralised Cardiac Safety

Abstract
Continual developments in technology are helping to provide solutions for the problematic issue of data inconsistency and inaccuracies in the analysis of Electrocardiograms (ECGs). Until recently, the use of a decentralised model was the main method of collecting ECG data, however this is now being replaced by a centralised approach which is increasingly being utilised throughout the industry. A new study of investigative sites conducted by the Tufts Center for the Study of Drug Development (CSDD) revealed that over 50% of respondents predict that over the next five years the increased usage of the centralised method will be significant. An explanation for this adoption of centralisation can be linked to the multiple advantages it offers in comparison to the decentralised approach. In addition to being more economically viable for companies, a critical advantage of this approach is that it offers greater consistency for clinical trials, while significantly increasing data quality.

An essential factor in assuring the adoption of the centralised model is the need for extremely compact instrumentation that can remove the problems associated with larger, more heavyweight ECG equipment typically used in the pharmaceutical industry. To achieve this and therefore make the implementation process easier for companies, hand-held ECG collection devices are now appearing on the market, facilitating a seamless integration of the centralised system with customers’ central databases.

Cardiac Safety
Research has shown that arrhythmias are just one of the many serious cardiac conditions that have an increased risk of occurrence as a result of certain drugs. The repercussive effect of this is that drug withdrawals from the market, labelling changes and the denial of regulatory approval for marketing most often occur due to issues relating to cardiac safety. All new drugs entering the market must therefore be subjected to exhaustive clinical testing prior to their release, to confirm they do not have a negative impact on the cardiac health of patients. Precise analysis, accurate collection and consistent interpretation of data are therefore vital. Facilitating this process for biopharmaceutical organisations, contract research organisations (CROs) and medical device companies are newly emerging electronic data capture and transfer technologies. These new technologies offer essential tools which enable trial sponsors to reliably evaluate the effect of investigational drugs on the electrical functions of the heart.

The Regulatory Perspective
Despite there being no current legislative mandate in place with regard to ECG assessment across clinical trials, the performance of a Thorough ECG Trial (TET) for new compounds has been stipulated as a key requirement by the US Food and Drug Administration (FDA) with a few limited exceptions. More specifically, the ICH E14 guideline was implemented with the intent of monitoring the QT/QTc prolongation in new drugs to ascertain their cardiac safety risks. The guideline also has an advisory function, specifying how best to conduct trials to determine the cardiac effects of a new drug.

A key requirement of the ICH E14 guideline is that a proof of concept, providing evidence that a centralised ECG system can be successfully used, must be done prior to the commencement of a TET trial. The guideline advises that if any cardiac safety concerns arise, a more thorough and intense ECG collection will be necessary for Phase III trials. A centralised method employs digital ECGs and a core laboratory, which deals with the majority of the work that would be handled by clinical trial sponsors, CROs and individual investigational sites. ECG equipment will be supplied by the core lab to investigator sites, demonstrating one of the key benefits of centralised methods: consistency. The centralised method promotes consistency through its focus on standardised data and quality controlled equipment and staff. Another advantage to using digital ECG data collection methods at the core lab is increased speed of the analysis process. In addition, the use of high resolution digital methodology eradicates transcription and misinterpretation errors that are typical of the decentralised approach, therefore producing more focused and consistent data.

Benefits of Centralisation
When a decentralised model is employed, ECG studies are conducted within a variety of investigator sites, using local ECG machines. Inconsistent results often occur as a consequence, due to different types of instruments using varying algorithms for calculations. In contrast, a centralised approach overcomes this issue of inconsistency by digitally collecting high quality data in a standardised format for assessment, with the use of consistent and validated systems. All interval duration measurements (IDMs) are assessed by a qualified individual, and every ECG is evaluated by a qualified cardiologist who is trained to follow standardised procedures which are continually validated through a quality control programme. As a consequence, time that participants previously would spend on site is significantly reduced. Additionally, centralisation facilitates proactive data monitoring and tracking, with demography and missing visits noted automatically, thereby enabling the collection of valuable data as studies progress.

With the adoption of a centralised method, clinical trial sponsors can utilise emergent technology, improving the quality and accuracy of data collated, lowering the time commitment of investigators and improving the general...
participant experience. As a result of employing these new technologies, investigator sites can collate immediate, consistent, accurate data, improving site operations for stakeholders and offering a better service and value to pharmaceutical companies. The centralised approach also eradicates issues such as data variability stemming from inconsistent ECG collection and evaluation methods, which are commonplace in paper-based decentralised studies.

Although the advantages of a centralised system are clear and well supported, it is still commonly believed that centralisation is not the most economical method. As a result, a decentralised ECG study model continues to be utilised throughout a large majority of clinical trials, with the use of multiple investigator sites employing local ECG machines.

Cost Implications

The slower conversion from decentralised to centralised ECG collection is largely based on the concern over the true costs of a centralised model. Estimating an approximate figure of how many ECGs are required ahead of a study programme is difficult, therefore making the appraisal of an accurate cost of centralised versus decentralised ECGs problematic. Unknown variables include staffing costs, the number of investigator sites and the number of ECG machines required. Sponsors commonly still maintain the understanding that a centralised ECG provider is more costly than a localised or internal method, primarily as a consequence of the hardware distribution involved. Recent research conducted by Tufts indicated that sponsors perceive centralised ECG providers to be more expensive, although they reflected that increased accuracy and accessibility of central providers more than substantiates the extra cost.

When a decentralised model is employed, the majority of collection, transcription and interpretation of ECG data is conducted by the sponsor and the individual monitoring site. As a result, the majority of companies working with this method perceive the core laboratory in a centralised system as a non-essential added expense. Contrary to this belief, a centralised approach has been proven to save costs. When using a decentralised approach, sponsors must pay a sizeable ECG acquisition fee which includes charges for technician time and the use of ECG machines at the investigator site. In addition, the expense for labour required for both the site and sponsor/CRO personnel to manually transcribe, double-data enter, monitor and quality control data from multiple sites is very high. These costly labour and associated fees are reduced when using a centralised approach. The Tufts report illustrates that sponsors are focused on this area and there has been a shift in the perception of a centralised approach, with 70% of respondents identifying the costs of using an ECG core laboratory as less than, or equal to, the costs of using paper.

The Importance of Innovative ECG Technology

Although the study findings have confirmed that centralisation offers key benefits over the decentralised model, clinical trial sponsors still have a strong requirement for efficient and innovative instrumentation to ensure accuracy, consistency and cost-effectiveness. With reference to the ICH E14 guideline, the effectiveness of the ECG database is reliant on the employment of contemporary equipment with the facility for digital signal processing, which ensures an efficient safety assessment of ECGs. With the development of new lightweight and compact ECG machines which have a significantly smaller footprint than existing systems, the challenges raised by previous heavy and expensive instrumentation are removed. The key advantages of the new ECG devices are that they are much easier to manoeuvre and less costly to ship and store, resulting in companies being more inclined to adopt the centralised system. In addition to their newly compact size, the cutting edge instruments are improved on a technical level, offering more consistency and improved accuracy while effortlessly integrating with computer systems through a web application.

Increasingly studies are required to provide digital ECG data to a central digital system for the purpose of regulatory inspections. This data can then be stored on a central system and analysed by regulators to assess data quality. While this is not presently a compulsory requirement within the pharmaceutical industry, the majority of clinical studies will submit their data. According to the Tufts research, only a third of investigative sites assessed are obtaining ECG data in electronic form. The arrival of new ECG machines will
facilitate the data submission process, with all data being stored centrally and information easily transferable to the database when needed.

Conclusion

Heightened awareness regarding the cardiac safety of drugs has sparked closer examination of all new compounds, with intense pressure being placed on the biopharmaceutical industry to supervise the potential influence of new drugs on the electrical functions of the heart. Despite a decentralised approach to ECG data collection being used at length within the industry, it is currently afflicted with multiple restrictions, including low accuracy, consistency and efficiency of ECG data. The application of the centralised model benefits the industry in a number of important areas, including data quality and data capture, the reduction of workload for sponsors and the ECG site, leading on to significantly lower overall costs. As made evident in the Tufts report, 97% of respondents rate the central labs as more accurate and 90% view them as more efficient.

The Tufts study provides evidence to suggest that the advantages of centralisation are increasingly more recognised, with respondents identifying core labs as an effective and preferable method for conducting ECGs. A correlation between the adoption of centralised cardiac safety assessment and that of blood work, lab work and electronic data in clinical trials is highlighted within the Tufts study. After an initially slow period of adoption, recognition of centralised solutions and their benefits has dramatically increased since the implementation of regulations and increased knowledge of the advantages by industry professionals. The implementation of the ICH E14 guidance indicates that despite there being no plans for ECG to be mandatory within the pharmaceutical industry, recognition of the value and advantages of ECG centralisation is continually increasing.

References