Research has shown that some drugs have the potential to pose a significantly increased risk of arrhythmias or other serious cardiac conditions. Cardiac safety is therefore the primary reason for drug withdrawals from the market, labeling changes and delay or denial of regulatory approval for marketing. As a consequence of these well documented concerns, biopharmaceutical organizations, contract research organizations (CROs) and medical device companies are required to provide quality electrocardiogram (ECG) data in the primary stages of drug development to ensure the most comprehensive and accurate assessment of a new drug’s effect on the electrical functions of the heart.

Centralizing the process of collection and standardization of quality ECG data and employing digital ECG systems and a core laboratory, not only reduces inconsistencies that may occur from site to site, but in addition helps to alleviate laboratory and site workloads.

Despite the many benefits associated with a centralized system, a large number of clinical trials (Phases I to IV) continue to use a decentralized ECG study model typically carried out across multiple investigator sites using local ECG machines. The basis for this adoption of a decentralized approach includes a lack of regulatory guidance and a widespread perception that centralization is not cost effective. This article will discuss the regulatory requirements in relation to ECGs and will highlight the benefits of a centralized versus a decentralized approach.

**Regulatory Overview**

Recent concerns over the cardiac effects of new pharmaceutical products have triggered greater regulatory scrutiny for all new compounds and final drugs prior to reaching the marketplace. While there is no legislative mandate in relation to ECG assessment across clinical trials, the requirement to conduct a Thorough ECG Trial (TET) for new compounds has been mandated by the US Food and Drug Administration (FDA) with limited exceptions.

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This is a result of the introduction of the ICH E14 guideline which was developed to assess QT/QTc prolongation in new drugs to determine cardiac safety risks.

The ICH E14 guideline recommends that a TET should be performed and if any cardiac safety concerns are raised, Phase II trials will require more robust or intense ECG collection. Unlike many other clinical trials, the TET typically uses a centralized system, which has proven to greatly improve the accuracy and reliability of ECG data in clinical trials. This centralized approach uses standardized digital ECG machines for collection and a centralized high resolution data analysis supplied by a core laboratory.

Why Centralization?

Traditional ECG data collection methods use a decentralized model, typically carrying out ECG studies across multiple investigator sites using local ECG machines. However, there are significant limitations associated with this approach. The use of different instrument types at different sites means that Interval Duration Measurement (IDM) data are often inconsistent since not all instruments use the same algorithms for calculating the resultant data. As a consequence, the over read of the ECG output is not consistent across investigational sites and additional fees are required for professional cardiologist over reads on a site by site basis. In general, data are collected at the beginning and end of the trial, which provides very little information about the cardiac effects of the chemical entity under investigation.

As individual monitoring sites are responsible for performing and acting upon the interpreted ECG data, the transfer of information can result in transcription errors and other unexpected results due to differences in site investigators’ ability to adequately interpret the data. From a purely clinical standpoint, Viskin et al.1 did a study that was published in Heart Rhythm in June 2005 to look at the competency of non-cardiologists, cardiologists, electrophysiologists and QT experts in assessing the QT interval measurement in a small sample of ECGs. The findings were striking in that non-cardiologists and cardiologists were found to be essentially equal in their inability to assess the length of the QT interval with an accuracy rate of 21% and 22% respectively. Electrophysiologists fared better at 62% and QT experts were correct 96% of the time. For the majority of clinical trials being conducted today, whether the investigator interprets the ECG or has a local cardiologist do the work for them, it is highly unlikely that accurate clinical signals will be detected. These factors, coupled with the lack of consistency amongst cardiologists in their ECG interpretation, makes analyzing any data obtained very difficult. A centralized approach has been found to efficiently overcome all the above shortcomings.

The Vital Role of Centralized ECGs

A centralized approach uses digital ECGs and a core laboratory which handles much of the work done by clinical trial sponsors, CROs and individual monitoring sites. The core laboratory typically provides investigator sites with all standard ECG equipment having first ensured that it has been tested to full functionality and is programmed for the correct demography capture for the particular study.

The use of digital ECG data collection at the core laboratory speeds up the analysis process and generates much cleaner data by using a high resolution digital methodology eliminating the common transcription and misinterpretation errors which normally occur when following a decentralized approach. In addition, some core laboratories employ systems that automatically check for missing visits or any changes in demography. Each ECG is evaluated by a qualified cardiologist at the core laboratory to ensure maximum data quality, integrity and consistency.

In the ICH E14 document, centralization is recommended in cases where cardiac safety concerns are raised. As such, the guideline further highlights the superior results generated by this approach. However, approximately two-thirds of ECGs collected in clinical trials are still obtained using traditional decentralized paper methods. The continued use of decentralized systems is partly due to limited regulatory mandates in this area and the misconception that centralized systems are more costly.

Cost Implications

Currently, there is much debate about estimating the true costs of centralized versus decentralized ECGs. Quantifying the number of ECGs that will be required in advance of a study program is particularly difficult, making it harder to estimate the true costs of centralized versus decentralized ECGs. Staffing costs, the number of investigator sites and the number of ECG machines needed are unknown and vary based on the specific study design.

Additionally, much of the collection, transcription and interpretation of ECG data is carried out by the sponsor and the individual monitoring site when using a decentralized model. This means that many companies...
using this approach see the use of a core laboratory in a centralized system as an unnecessary additional expense. However, added costs in a decentralized model include fees which are paid to the site, including a technical fee for the ECG acquisition and a professional fee for evaluation of the ECG. These fees are based on standard medical reimbursement rates (CPT codes). In many settings, where a qualified cardiologist is not available, the site needs to employ the necessary qualified expertise which can generally cost from $75 to $250 per ECG.

Centralized ECG trials involve the rental, storage and shipping of the ECG machines to each investigator site. A typical ECG device can weigh anything between seven to 10lbs and can be of substantial size, which means they can be expensive to transport and store. Furthermore, the maneuvering and preparing of the instruments ready for use can be time consuming and difficult for inexperienced users. The average rental cost of such a machine generally varies between $100 and $150 per month. Reducing the acquisition fee, which includes the amount of rental paid for the ECG instrumentation, is one way of lowering costs. This point is further explored below.

However, the added value of digital ECG collection, improved accuracy and reliability can actually help sponsors reduce costs. By eliminating errors in collection and transcription of ECG data, sponsors can reduce the amount of retesting that must be carried out. In addition, the centralization of ECG analysis eliminates these unnecessary over read fees and also allows a reduction in the standard site fee payments for the technical fees. For example, analysis of blood tests in clinical trials was originally decentralized and required the management of site-specific laboratories with multiple normal ranges, data quality issues and high costs due to site specific requirements. When blood work is performed in a centralized manner by experienced core laboratories, an efficient, consistent and high quality service is offered. Also, since the use of centralized equipment is an integral feature of a core laboratory, sponsors should not technically have to pay extra for machine rental.

The Future of Centralization

Although centralization provides clear advantages over the decentralized model, there is still a clear need for innovative new instruments which can help sponsors increase accuracy, reliability and cost effectiveness, while overcoming the perceived challenges of decentralization. The issue of large, heavy and expensive instrumentation could be tackled with the introduction of highly compact ECG machines that have a much smaller footprint than existing systems. A number of new highly-compact ECG machines on the market have already made several strides towards this goal, being a fraction of the size of traditional machines and still provide full ECG functionality. These smaller machines are easy to maneuver and are less expensive to ship and store.

Advances in software allow these new instruments to integrate into existing computer systems allowing key data, such as demographics and algorithms, to be automatically downloaded prior to a trial. The ability to download these data is a substantial benefit in terms of both staff time and cost, especially to sponsors involved in studies involving non-cardiac drugs where the investigator site is not familiar with ECG systems.

Traditional ECG machines produce a paper printout of all the key ECG data which are then transcribed and the results analyzed. However, errors are common during transcription which leads to inaccurate results and has a detrimental effect on the overall validity of the trial results. Eliminating the need for this printout by enabling the machines to upload the data directly onto the core lab computer system would eliminate transcription errors and increase the overall accuracy and timeliness of the data, as well as saving staff time and cost in the process.

Regulators are increasingly requesting that studies submit digital ECG data to a central digital system, also known as a data warehouse, to assist with regulatory inspections. All data stored on the system can then be accessed by regulators to quickly and efficiently analyze the quality of the data. Even though this is not a mandatory requirement as yet, most clinical trial sponsors are currently complying with it. A centralized digital ECG system makes this request easy to comply with as all data are already stored centrally and simply have to be transferred to the database as required.

Conclusion

An increase in concern over the cardiac safety of drugs has resulted in heightened regulatory scrutiny for all new compounds and has put greater pressure on the pharmaceutical industry to monitor the potential effect of new drugs on the electrical functions of the heart. Although the use of the decentralized ECG study model is still widespread across the industry, it suffers from a number of limitations including poor accuracy, reliability and efficiency of ECG data. The introduction of the centralized model of ECG has provided the industry with significant improvements in a number of key areas including data quality and data capture in addition to reduced workloads for sponsors and the ECG site, thus lowering cost while increasing data quality.

By utilizing new ECG solutions, clinical trial sponsors can benefit from a more cost effective and efficient system that will help them to ensure patient safety and regulatory compliance by reducing site burden and increasing accuracy, reliability and usability. Although there are no plans at the moment to enforce centralization as standard within the pharmaceutical industry, the ICH E14 guidance highlights centralization as a more robust method of ECG data collection. Though the advantages of a centralized ECG system are clear to see, demonstrating the real value of this approach remains a challenge. However, it is evident that when all the costs are added up, the advantages of centralization are unrivalled by decentralized systems.

Reference:

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