

Highly Automated ECG Analysis

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The finalization of the International Conference on Harmonization (ICH) E14 “Guidance for Industry: Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs” in 2005 changed expectations for evaluating cardiac safety in pharmaceutical development¹. This guidance was created after several compounds linked to the potentially fatal cardiac arrhythmia, Torsade de Pointes (TdP) caused by prolongation of the QT interval on the ECG, were withdrawn from the market. Central to the implementation of E14 is the Thorough QT/QTc trial (TQT), a study dedicated to assessing the effects of drugs on the QT interval. This study is now required by regulatory agencies for essentially all compounds that can be administered to healthy volunteers. The objective of the TQT is to determine if the study drug prolongs the QT interval by small degrees in healthy volunteers that may predict larger, more dangerous QT prolongation at higher exposures, in cases of underlying cardiac disease or drug interactions in patients. The threshold of regulatory concern is described in the guidance as a change relative to placebo of about 5 milliseconds (ms) defined by a single-sided upper 95% confidence interval of less than 10 ms¹. Compounds that are associated with QT prolongation above this threshold will then likely require extensive ECG assessment in later stage development to further assess the compound’s potential to prolong the QT interval.

The ability to identify such a small change in an interval that is about 325 to 450 ms in duration and may vary by more than 60 ms/day in a normal person requires exquisite study site execution and precise ECG analysis². When E14 was finalized in 2005, the ECG analysis requirement was naturally filled by existing ECG Core labs that had developed to centralize ECG data acquisition and analysis for large, global, late stage trials. In this ECG Core lab model, significant resources are required for managing large equipment inventories, equipment deployment and retrieval, multilingual technical support, ECG acquisition and cardiologist review of every ECG. Currently, ECG Core labs follow a similar model for provisioning much smaller, usually single site TQT trials. The clinic acquires the ECG data and sends the data to the core lab where each ECG is reviewed by a cardiologist.

The increased scrutiny of ECG data has prompted an evolution in study execution, ECG acquisition technology and ECG data analysis in the past decade. E14 was purposely non-prescriptive so that collaboration between the regulatory agencies, sponsors and ECG Core labs could improve the process as more experience was gained. One example of such a process change has been the increased focus on executing clinical trials to ensure high quality ECG data³. Study execution has been greatly enhanced by the use of 12-lead Holter ECG technology rather than stand alone ECG machines. Several studies have shown that both modalities provide similar results while Holter technology markedly decreases the resources required at the Phase I unit and core lab to acquire and process the data^{4, 5}. Another example is the change in baseline performance in TQT trials. Initially, it was thought that collecting ECG data at 10 to 14 timepoints over a 24-hour period prior to dosing was necessary to minimize variability. However, the use of a truncated baseline consisting of three replicate ECG recordings rather than 24-hour baseline for crossover studies is now widely accepted. This change in baseline definition has decreased cost without impacting QT data quality and may actually decrease variability^{6, 7}.

Yet another example of science changing how QT data is analyzed is the trend in the use of various QT correction factors over the last decade². Bazett’s heart rate correction (QTcB) was the most commonly used clinical correction for decades, but has marked limitations and was originally suggested as the correction factor for TQT studies. Early on there was a migration away from the use of QTcB in the primary analysis of a TQT to use of an individualized correction factor (QTcI). However it appears that QTcI provides little, if any benefit over Fridericia’s correction (QTcF) in a standard TQT conducted in healthy normal volunteers⁸. It has been suggested that QTcI may even be more inaccurate than QTcF if an adequate range of heart rates is not provided to build the correction factor model⁹. The number of baseline ECG recordings required to generate a QTcI make this approach much more expensive. These disadvantages have made QTcF the preferred correction method in most situations.

The trend that will ultimately have the greatest impact upon the analysis of TQT studies is the expanded role of computer algorithms in ECG interval duration measurements. In true manual measurement the measurement calipers are placed manually by a cardiologist or technician. Though once frequently used, fully manual methods have been largely supplanted by the semi-automated method, also called manual adjudication, for reviewing ECG recordings. In this method an algorithm first places the calipers for ECG interval measurements which are then confirmed or modified by a cardiologist. This model is appropriate for late stage trials where patients often have abnormal ECG recordings which can be difficult for automated algorithms to accurately interpret waveforms¹⁰⁻¹². However, advances in measurement algorithm technology have reduced these inaccuracies. For example, the generation of a single beat to represent all the QRS complexes in each lead of the ECG and superimposition of these 12 representative leads, or the generation of a single representative beat for all 12 leads, has decreased the impact of artifact and improved user interface^{13, 14}. Some studies have even shown newer automated methods to have even less variability than semi-automated methods in healthy volunteers participating in a TQT¹⁵. However, even with these advances most measurement algorithms still have a higher level of inaccuracies when ECG recordings are not normal, see Figure 1^{11, 16-18}. Thus although the semi-automated method is still resource intensive and adds significantly to the cost of the analysis, it appears justified when evaluating ECG recordings from a patient population. This reluctance to use fully automated review has carried over into TQT trials involving healthy normal volunteers where algorithms are much more accurate.

The highly automated approach has been developed as a cost effective approach to mitigate the concerns with fully automated review in healthy normal volunteers. In this approach, the computer algorithm measures all intervals similar to the initial steps in the semi-automated method. However, the algorithm has the ability to identify characteristics, such as T wave abnormalities, that may impact the accuracy of the automated algorithm^{10, 12}. Those ECG recordings having such characteristics are then be reviewed by a cardiologist. This method is well suited for evaluating normal ECG recordings from a healthy normal volunteer population. The automated component of the method significantly decreases costs and time associated with data review but provides the added assurance that the small percentage of ECG recordings at risk for

inappropriate automated classification will be reviewed by a cardiologist.

In addition, manual extractions of 10 second ECG recordings from Holter recordings for interval duration measurement are time consuming and can't fully assess preceding heart rate stability which has a major impact upon the QT interval. So computer algorithms have been developed to automatically extract the ECG recordings from time windows around the nominal time point for ECG acquisition based upon stable preceding heart rates and minimal artifact. One such algorithm has been shown to significantly decrease variability in ECG data¹⁹ while minimizing human resources and providing data faster.

The Hybrid Phase I/ ECG Core lab

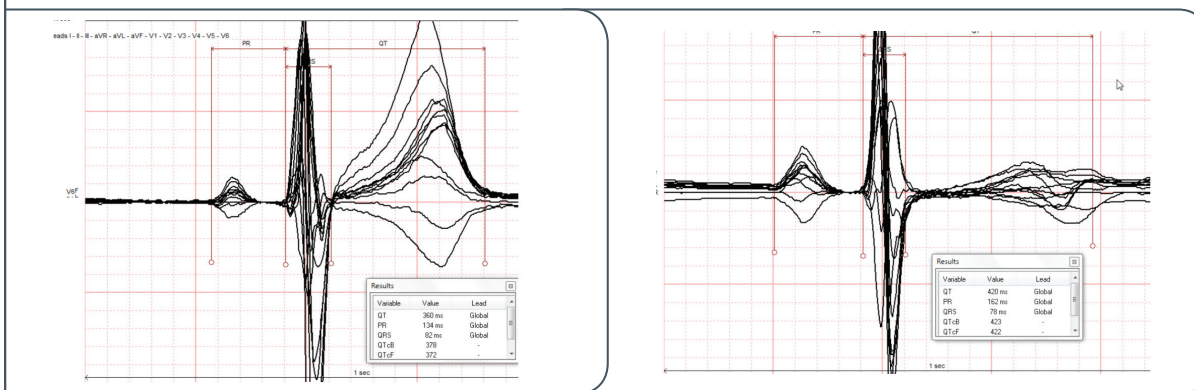
Based upon the knowledge gained from conducting more than 36 TQT studies and 140 studies with intensive ECG monitoring, Celerion has developed a Hybrid ECG Core lab that fully integrates the core lab and clinic functions. Extensive experience in early cardiac safety services has allowed us to carefully define where efficiencies could be realized in a dual functionality organization. This new type of core lab provides a single entity for sponsors to work with and minimizes inefficiencies associated with separate management of the two functions.

Since Celerion was able to develop the Hybrid Phase I/ ECG Core lab from the ground up, it was possible to streamline the structure. Celerion did not have a legacy of equipment inventory or systems based upon software optimized for late stage trials. For example, equipment costs were reduced by the use of a single device to function as a stand alone ECG machine and Holter monitor. Equipment inventory and logistics are limited to that required to service our four Phase I units. The units are familiar with the equipment so extensive technical support is not required. Ancillary services such as strategic planning, regulatory support, data management, medical writing and biostatistics are not duplicated.

By implementing the latest in ECG processing solutions, Celerion is able to maximize automated processing while maintaining cardiologist overview of recordings where required to ensure the highest quality. Automated extraction of ECG recordings for measurement not only reduces cost, but improves quality.

In developing this new type of core lab Celerion has implemented two cutting edge technologies: Bluetooth enabled Holter monitors and highly automated review of ECG recordings.

Figure 1. On the left is a normal ECG represented by superimposition of the 12 representative beats that is accurately measured. Note the monophasic T waves in all the leads. On the right is a similar representation of an ECG with biphasic T waves that resulted in an inaccurate automated measurement. This ECG was pulled up for physician review due to the T wave abnormalities.



Bluetooth enabled Holter monitors

The Global Instrumentation M12R Holter monitor acquires up to 48 hours of continuous ECG recordings at 1000 samples per second. Bluetooth communication with a computer allows visualization of the 12-lead ECG during an ongoing Holter recording session. This is unlike the “blackbox” approach with most Holters where quality cannot be assessed until the recording is complete and a separate stand alone ECG machine is required to perform safety ECG recordings while Holters are being acquired. In addition, loss of data is possible with a telemetry system when a subject inadvertently strays outside of antenna range is prevented because the recording is stored on an onboard SD card. The M12R can also be used as a stand alone 12-lead ECG machine when not functioning as a Holter.

As the equipment and software are all an integral part of Celerion, the data is uploaded directly into our own IT systems eliminating the need for FTP servers or couriers of data. In addition, the subject data is preconfigured on a PC and transmitted to the Holter recorder which decreases error rates.

The highly automated approach

The highly automated approach to ECG review makes use of integrated software solutions from Global Instrumentation LLC and AMPS LLC. The focus was

on developing tools to take advantage of automation in order to reduce resource requirements and potential for error. The data is first acquired using the Global Instrumentation M12R Bluetooth-enabled Holter monitor. Data is subsequently uploaded to a computer where AMPS Antares® software automatically extracts heart rate and artifact optimized 10-second 12-lead ECG recordings around pre-specified timepoints. This tool has been shown to significantly decrease variability in ECG data¹⁹. Subsequently AMPS FAT QT analyzes and measures the recordings and assesses for the need for physician review. Most recordings will be automatically processed into the database with automated measurement annotations. A small percentage requiring cardiologist review will be reviewed using a standard semi-automated approach through AMPS TrialPerfect. Quality assessment of cardiologist review is automated within the TrialPerfect system.

The introduction of the Hybrid Phase I/ ECG Core lab clearly establishes Celerion as the world leader in innovative early cardiac services.

This highly automated approach to ECG data review will enable Celerion to provide high quality ECG data at a significant cost and time savings to sponsors thus allowing for faster development decisions.

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