AMPS-QT

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AMPS-QT is a quarterly journal dedicated to all the people and organizations involved in the world of cardiac safety. Published by AMPS LLC, it covers all aspects of methodology and software technology related to clinical trials and Thorough QT studies.

Editorial

In the 3rd issue of AMPS-QT (3Q09) we reported on the industry's acknowledgement that a change of gear was necessary to successfully survive and grow, but also that the sponsors appeared reluctant to take the risk and test new technologies, to avoid the risk of wasting resources and lose credibility.

The recent announcement by Celerion, and the demonstration provided by Spaulding Clinical at the last DIA Annual Meeting on June 13-17 indicate that the industry is indeed developing, innovating, and finding new ways to provide leading-edge, faster, and cheaper ways to perform clinical trials and T-QT Studies. Spaulding Clinical's concept is currently being developed and we hope to provide an exhaustive article in the next AMPS-QT. In this issue we welcome a paper by Dr William Wheeler MD, FACC and Joy Olbertz, PharmD, PhD; both at the origin of the new concept, launched by Celerion: The Highly Automated Hybrid Phase I/ECG Core Laboratory. For the people who don't happen to know Dr Wheeler and how he could have come-up with such a concept we can say that after a very successful career in direct patient care at Cedars-Sinai Medical Center in the early eighties, having saved countless lives, he made a transition into clinical research, ultimately landing at Quintiles, the largest CRO (clinical research organization) in the world, as medical head of their cardiovascular therapeutics program. Having achieved great success there, and on track to a spectacular career, he instead decided to challenge himself again by joining a startup biotech company as their chief medical officer. Again, he thoroughly distinguished himself by guiding their technology from molecule, through human trials, to investor exit. Dr Wheeler then moved to Seattle, WA, to accept the prestigious role of Chief Medical Officer of SpaceLabs, a major international provider of cardiovascular research services to the pharmaceutical and medical device industry. Dr Wheeler then moved to MDS Pharma Services, a quality provider of pharmaceutical research solutions ranging from molecule to market, as head of their global cardiology services, and eventually, through the Celerion acquisition, he is today Therapeutic Area Lead-Cardiovascular at Celerion, where together with Dr. Joy Olbertz developed and implemented the very interesting concept described in the article. Enjoy!

A Noteworthy Contribution:

The Highly Automated Hybrid Phase I/ECG Core Laboratory

By William Wheeler, MD, FACC and Joy Olbertz, PharmD, PhD; Celerion, Lincoln, NE.

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 development (1). This guidance was created after several compounds were withdrawn from the market when linked to the potentially fatal cardiac arrhythmia, Torsade de Pointes (TdP) that can be caused by prolongation of the QT interval on the ECG. 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 most regulatory agencies for almost all compounds. The objective of the TQT is to determine if the study drug prolongs the QT interval by small degrees that may predict larger, more dangerous QT prolongation at higher exposures or in cases of underlying cardiac disease or drug interactions.

The threshold of regulatory concern is described in the guidance as a change relative to placebo of about 5

milliseconds (ms) with a single-sided upper 95% confidence interval of less than 10 ms. Compounds that are shown to produce QT prolongation above this threshold will then likely require extensive ECG assessment in later stage development to further assess the compounds potential to prolong the QT interval (1). 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 is difficult (2). The QT measurement varies in response to a wide range of stimuli and this variability is a main determinant for the major cost driver of TQT studies, sample size. Advances have been made in clinical study execution since 2005 to help minimize variability (3).

When E14 was finalized in 2005, the ECG analysis requirement was naturally filled by existing ECG Core labs. These late stage oriented ECG core laboratories modified their processes to accommodate ECG recordings from TQT studies. The typical ECG core laboratory was designed to service large, global trials that may involve hundreds of investigative sites. In addition, patients in these studies have a high incidence of abnormal ECG recordings that do require a cardiologist to read them. These studies often are of long duration with relatively slow acquisition of ECG recordings. ECG core laboratories typically have large overhead due to the need for large inventories of ECG machines, logistics to deal with shipping, customs, equipment return, multilingual technical support and repeated site training necessary for large late stage clinical trials. In the standard ECG core laboratory structure, the actual processing of the ECG is a small proportion of the cost of doing a study. Recent data from one ECG core lab revealed that ECG processing (extraction and reading) was less than 8% of the ECG core lab cost (4). Since typically execution of a TQT requires both an ECG Core Laboratory and a Phase I clinic much of the additional costs represent redundant activities for each project team including; study management, project management, and equipment management.

The Hybrid Phase 1/ECG Core Laboratory

A recent concept is the merging of the Phase I unit and the ECG Core Laboratory into a single functional unit, a Hybrid Phase I/ECG core laboratory. Much of the infrastructure necessary to perform large, global, late stage trials is unnecessary in such an organization focused on phase I clinical research. Overhead items such as large inventories of ECG machines, logistics to deal with shipping, customs, equipment return, multilingual technical support and repeated site training are not necessary. In addition, a hybrid organization can also make the process more efficient by eliminating duplication of activities such as project and data management. Potential conflicts and communication problems are minimized by fully integrating the ECG Core lab into the Phase I clinic structure reporting through a single management structure. As the overall infrastructure of the organization is decreased, processing ECG recordings becomes a larger component of the fixed cost (5).

Costs can be further reduced with more automation in the processing of ECG recordings. Currently most ECG Core laboratories use a semi-automated method for ECG reading in which a computer algorithm performs the initial measurements. Cardiologists then review all the ECG measurements and either confirm or change them. This model is based upon the later stage trial enrolling patients, a significant percentage of whom have abnormal ECG recordings and require confirmation. However, computer algorithms to perform ECG interval duration measurements have improved markedly in the last several years, especially when analyzing ECG recordings from healthy normal volunteers, but still errors in measurements are made. These errors are infrequent in normal ECG recordings without significant artifact but are more common in abnormal ECG recordings (6, 7, 8, 9). Although the incidence of these errors is low, they have slowed the adoption of a fully automated approach to ECG interval duration measurements. This is despite the fact that several studies have shown similar or less variability with automated measurements than the semi-automated method even with these errors (9, 10, 11).

A highly automated approach combines the best of semi-automated and fully automated processing of ECG recordings. In the highly automated approach, a computer algorithm automatically performs the ECG interval duration measurements. Then using a tool such as the AMPS FAT-QT application, ECG recordings are evaluated for characteristics known to impact the ability of an algorithm to accurately measure ECG interval duration such as abnormal T waves. Normal ECG recordings without these characteristics are automatically confirmed and added to the data base. ECG recordings exhibiting such characteristics are put in a queue for the cardiologist to read using a standard semi-automated approach. Because only about 10% of the ECG recordings are flagged for cardiologist review, the cost associated with ECG review is greatly reduced.

FAT-QT is a highly configurable tool. In this process multiple parameters can be selected such as heart rate, QT/QTc intervals, low or high frequency noise, QRS

regularity, and T wave characteristics such as amplitude and complexity. T wave complexity is particularly effective in capturing those ECG recordings that may have biphid or biphasic T waves. These types of abnormal T waves are common in subjects that receive moxifloxacin in a TQT and are associated with a higher percentage of measurement inaccuracies. However, in using a conservative approach to identify ECG recordings for cardiologist review most of the ECG recordings from standard TQT studies were accurately measured automatically. Occasionally the ECG recordings were inadequate for measurement and then excluded from the data analyses. In only rare instances did the algorithm incorrectly measure an ECG in an otherwise technically adequate recording.

Another process that can be automated to decrease cost is the extraction of 10 second, 12 lead ECG recordings from a time window around the nominal timepoints in the study. Manual ECG extraction is time consuming and cannot accurately assess stability of the heart rate preceding the extraction. Unstable heart rates are confounded by hysteresis and cause increased variability in the measurements. Antares can be used to automate this process. It assesses preceding heart rate stability and artifact to provide a configurable number of replicates from within the designated time window and has been shown to decrease QT data variability (12).

In addition, generation of a representative beat from each of the 12 leads and superimposition of those 12 leads for display to the reader has also significantly reduced variability as well as facilitating faster ECG data review (13).

In summary, the Highly Automated Hybrid Phase 1/ECG Core laboratory approach can reduce the cost of TQT execution and analysis through more efficient execution and lower overhead by maximizing the potential for automated ECG review, minimizing the requirement for cardiologist review, and reducing overall QT data variability thus minimizing sample size requirements.

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Products News

Looking forward
In July AMPS is planning to release a major update of:

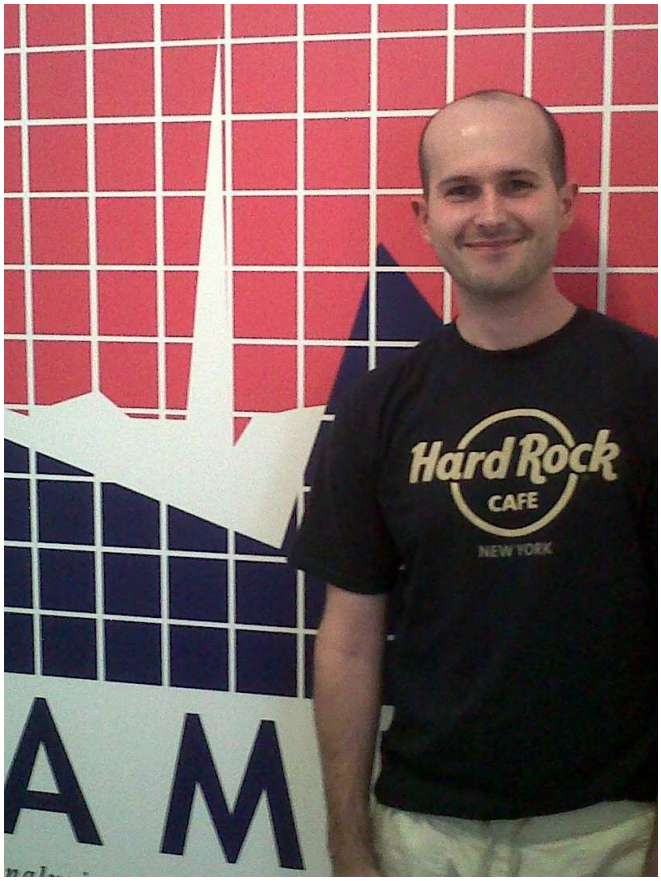
- FDAEcg Suite v.2: enhanced graphical interface, with advanced scoring display, new scoring metrics and optimized ECG management.

AMPS Notebook

AMPS will be present at the 37th Computing in Cardiology Conference held in Belfast, Ireland at the end of September.
Fabio Badilini and Martino Vaglio will be presenting the basic concepts of their paper entitled "Use of ECG quality metrics in clinical Trials".

AMPS people

We continue our round of staff introductions with Claudio Baratti.
Claudio, started his Computer Science studies in Italy at the University of Milan where he obtained his Bachelor's degree in 2003. He joined AMPS in 2005 and since then he is the leading developer of TrialPerfect.
Claudio is an expert in database management and web site development; he is also the AMPS website administrator.



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