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

After the announcement and the release of the first issue of AMPS-QT we received numerous requests from various parties to be included in the distribution of the future issues. We take this as a positive signal of interest both on AMPS and its technology, and on the scope of the magazine which, we reiterate, aims to be a mean for opinion exchange and general information about cardiac safety. In this respect in this issue we welcome a contribution by Dr. Nenad Sarapa, a world recognized thought leader in cardiac safety, well known for always searching for the truth, and not just an answer. His insights have always been very helpful and we are proud to publish his essay.

We remind our readers that contributions and ideas for articles, as well as comments on published ones, are welcome, please send them to: AMPS-QT@amps-llc.com.

A Noteworthy Contribution:

Quality assessment of digital annotated ECGs in clinical trials: potential value of the FDAEcg Suite™

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Drug-induced QTc prolongation is a common reason for the termination of development of drug candidates or the delay in regulatory approval and precautionary strict labeling, because it is associated with the risk of torsades de pointes potentially leading to sudden cardiac death. While the thorough QTc study (TQTS) is the mainstay of the conclusive assessment of the drug's liability to cause proarrhythmia at the low threshold of regulatory concern defined in the ICH E14 guidance (5-10 ms), pharmaceutical sponsors today perform robust QTc assessment even earlier in clinical development by acquiring serial digital triplicate ECGs under rigorous experimental conditions in Phase 1 studies in healthy subjects. These studies can reliably detect a clinically significant QTc prolongation. Drug candidates that cause QTc prolongation in Phase 1 and TQTS may progress into Phase 2/3 clinical trials if they offer therapeutic benefit in unmet medical needs, in which case the robust ECG monitoring must be continued in all pre-approval clinical trials. Being expensive and effort-intensive, the robust ECG assessment imposes significant demand on the proverbially scarce R&D resources in drug development, and pharmaceutical sponsors stand to greatly benefit from approaches that would reduce the cost while retaining the precision and quality of ECG analysis in clinical trials.

Digital ECG has become the dominant modality of acquisition, processing, measurement, storage and regulatory submission of ECGs from clinical trials. The US Food and Drug Administration (FDA) mandates that ECG data within the NDA be submitted in digital form with annotations detailing the exact onset and offset points of ECG intervals. HL7 version 3.0, based on the Extended Markup Language (XML) standard, was adopted for the definition of all data types necessary to describe digital ECG waveforms and annotations. The HL7 v.3.0 standard meets the requirements for the regulatory submission of aECG from pharmaceutical clinical trials as well as the exchange of aECG data between CROs, sponsors, regulators, hospitals and academia. The intent of the FDA digital ECG guidance was primarily to verify the quality of the digital annotated ECG (aECG) data analysis from the TQTS stored in the FDA Warehouse of digital ECGs, although the Agency has also occasionally requested submission of aECGs from Phase 1, 2 and 3 studies. ECG data quality critically influences the ability of a clinical trial to detect small drug-induced QTc prolongation, because poor ECG signal quality is an important confounding effect for the precision of fiducial mark placement during QT interval measurement by both the readers at the central ECG laboratory and the fully automated algorithms. ECGs

with very high noise content will be present in ECG data from every clinical trial including TQTS, particularly when the conditions during ECG acquisition are not rigorously controlled. The low frequency (LF) noise is associated with baseline wander or drift in the ECG, possibly associated with poor skin-electrode impedance, while the high frequency (HF) noise is typically associated with artifacts originating from non myocardial sources (e.g. skeletal muscle tremor, respiration, other mechanical activity). While the noise content depends on the quality of ECG acquisition at the study site, central laboratories do not report the number of noisy ECGs per study that were incompatible with reliable manual QT measurement, and were found to annotate QT interval in ECGs of unacceptable quality. Moreover, QT measurement by human readers at the central laboratory has inherent within-reader, between-reader and day-to-day variability as well as a certain degree of measurement error despite the high resolution digital on screen settings. In healthy subjects with normal ECG waveforms, the fully automated analysis by the ECG recorder's algorithm could produce QT/QTc data of equal value to those from the central ECG laboratory, thereby reducing the cost of robust QTc monitoring in Phase 1 studies, as long as the fully automated readings could be trusted on basis of the verified quality of ECG data. Given that the FDA would accept QT/QTc data measured by all available methods, the use of fully automated analysis by the ECG recorder in TQTS could further reduce the cost of QTc assessment in drug development. Since patients with the target indication often have abnormal waveforms that impair the precision of the fully automated analysis, the ECGs from Phase 2/3 clinical trials should be analyzed by the cardiologists at the central ECG laboratory whenever the QTc prolongation or the cardiac safety outcome is an important objective of such later phase trial.

The FDA medical reviewers currently use the FDA Warehouse of digital annotated ECGs to evaluate the quality of aECG data during the NDA review. They either visualize ECG waveforms with annotated intervals at random, or identify the outlier aECGs that warrant scrutiny based on the scores for quality metrics produced by the Warehouse algorithms. The FDA medical reviewers will initially assess a relatively small number of aECGs randomly chosen from all parts of the data base to understand the overall quality, looking primarily for noisy recordings with low T-waves. Subsequently, the FDA reviewers would spot-check the aECGs using the QT bias metric to explore how the central laboratory has assigned the fiducial marks of ECG intervals of interest. Lastly, the FDA medical reviewers target specific ECGs of interest for a closer look, after identifying them as outliers in the statistical results, or due to intriguing waveform descriptions or other relevant criteria.

Table 1. Metrics available from the FDA aECG Warehouse.

Overall study summary
Total subjects in the study
Total ECGs in the study
ECGs per subject
Subjects with fewer ECGs
Subjects with more ECGs
ECG signal acquisition quality
ECGs with lead fail
Global LF noise level
Global HF noise level
QT annotation protocol adherence
ECGs without QT annotations
ECGs with QT annotations in multiple leads
ECGs with QT annotations not in primary lead
ECGs without expected number of QT's in primary lead
ECGs without expected number of QT's
ECG signal quality around the areas critical for precision of QT annotation
T-wave signal strength
T-offset LF noise
T-offset HF noise
T-offset S/N ratio
ECGs without expected number of QT's
ECG interval annotation by the Warehouse
QT bias
T-offset bias

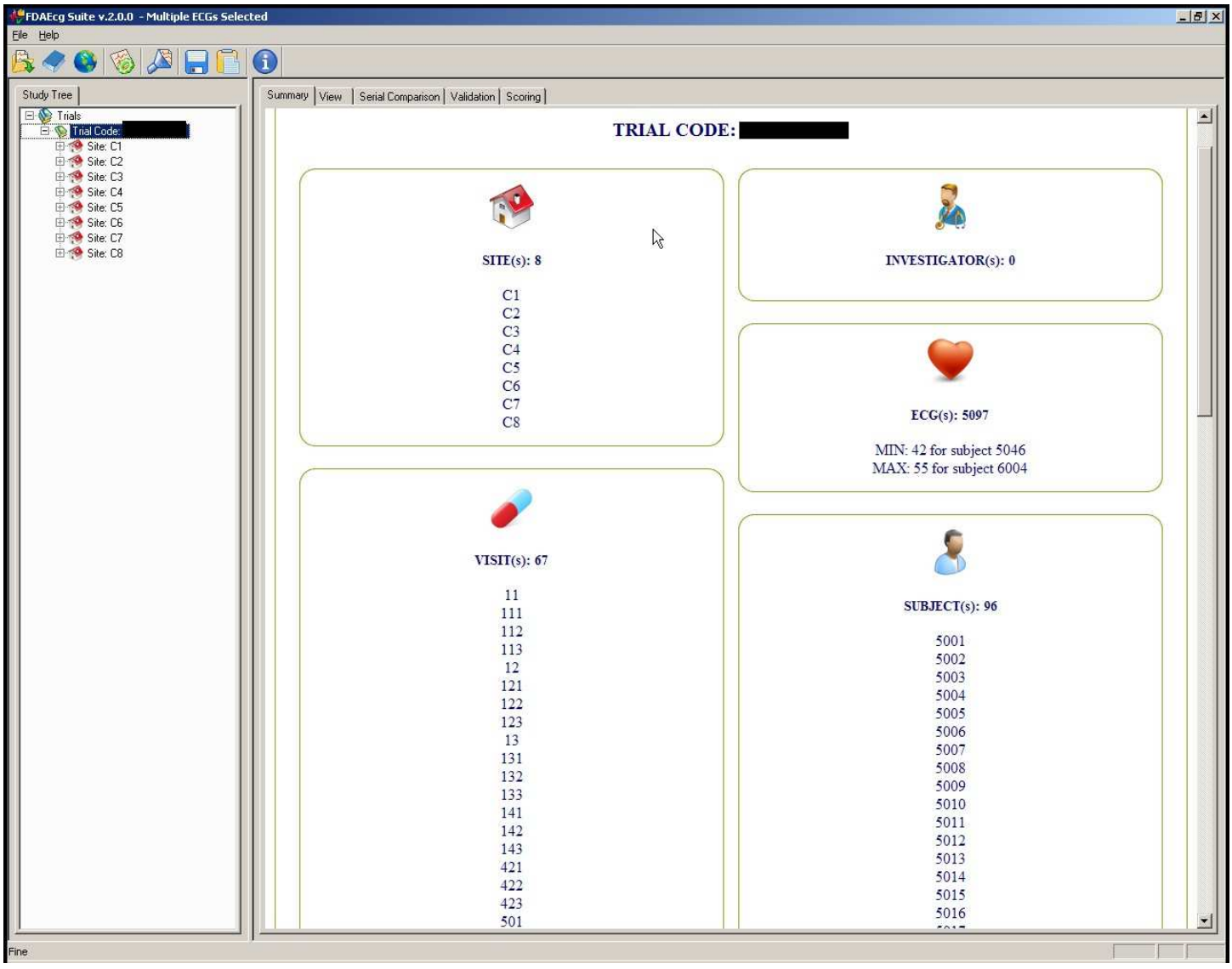
Legend: LF = low frequency; HF = high frequency; S/N = Signal-to-Noise ratio

Individual aECGs are assigned quantitative scores by the FDA Warehouse algorithms proprietary to Mortara Instrument applicable to different metrics presented in the Table. For every aECG in the FDA Warehouse, the relationship of the metric score assigned to the ECG versus the Warehouse threshold for questionable quality allows the FDA medical reviewers to easily navigate to specific aECG that merits closer attention. The Warehouse scores for the global LF and HF noise metrics illustrate the overall aECG signal quality, independent of how precisely the individual ECG intervals were annotated by the central laboratory, or by the fully automated methods. In contrast, the low value and/or low ranking for the scores of the T-offset LF and

HF noise and the T-wave signal strength point towards the ECGs of questionable quality that should have been excluded from analysis, and higher proportion of aECGs with such scores could reflect poorly on the performance of the central laboratory and the credibility of the fully automated methods. The QT bias and T-offset bias metrics are produced by the fully automated Veritas™ algorithm that determines the QRS onset and T offset within the Warehouse so that for each aECG, the difference between QT interval duration measured by the central laboratory and by Veritas™ becomes apparent to the FDA medical reviewers. If good agreement for the QT measurement by Veritas™ and by the central laboratory or the fully automated methods is shown by the QT bias and T-offset bias metrics, potentially confirming the reliability of the given methodology for detecting small drug-induced QTc prolongation.

If significant problems are detected with the quality of ECG data in the NDA and the performance of QT interval measurement by the sponsor's chosen methodology, the FDA reviewers would notify the sponsor of the need for remedial action resulting in the delay in NDA approval and, at least in theory, a possible non-approval. In light of this, the pharmaceutical sponsors could greatly benefit from the availability of quantitative methods to assess the ECG data quality and the credibility of QT interval measurement before they submit the aECGs from clinical trials to the FDA Warehouse. One such method is the *FDAEcg Suite™* from AMPS-LLC, a Microsoft Windows-based desktop digital application that enables users to display, review and score the annotated ECG data from clinical trials as well as validate the compatibility of XML ECG files with the HL7 v.3.0 format or other applicable ECG data standards.

The FDAEcg Suite™ display module is highly detailed and includes a customizable graphical interface and the ECG waveforms can be visualized in several formats (single lead,



superimposed leads, 3x4 and others). The display module also allows the user to visualize the ECG interval annotations on cardiac beats whenever they are available in the ECG XML file handled by the FDAEcg Suite™.

On the main user interface dashboard, the FDAEcg Suite™ produces an overall study summary with the number of aECG in the clinical trial and each treatment group and the summary statistics for each quality metric, with the option to drill down to separate listings of results in each data set. A computer screen shot of the FDAEcg Suite™ dashboard is presented in the figure in the previous page.

The FDAEcg Suite™ scoring module assesses the quality of the ECG according to a default set of built-in metrics, but other user-specific metrics can also be implemented through an open interface. The metrics computed in the FDAEcg Suite™ reflect the scores for different levels of the high frequency, low frequency and all-frequency noise derived by non-parametric methods involving a multi-step ECG signal processing. In addition to the noise-based metrics, the FDAEcgSuite™ can also compute the scores for the Heart Rate and T-wave amplitude metrics. For each metric, the FDAEcg Suite™ also ranks individual aECGs in the order of increasing score and displays the distribution of individual aECGs on histograms with thresholds marking the cutoff values for questionable vs. acceptable quality. The aECG waveforms could be viewed by double-clicking on the identifier in the table and the score values associated with the aECG distribution are visible by hovering the mouse pointer over the histogram displayed on screen. The thresholds for each quality metric were chosen empirically by AMPS-LLC based on the range of abnormalities observed in the Company's database of approximately 300.000 digital ECGs from healthcare and clinical trials (including TQTS, robust Phase 1 studies with triplicate ECGs and late phase trials in patients). The user-specific metrics can also be implemented based on the specific type of ECGs or trial population included in the AMPS-LLC database.

The FDAEcg Suite™ validation module is used to check for the proper HL7 v.3.0 semantic structure of the XML files. The proper format of an XML document is a necessary condition for submission of the digital annotated ECG to the FDA Warehouse by means of uploading the file on line on the web site maintained by Mortara Instrument on behalf of the FDA. The FDAEcg Suite™ provides user-friendly interface support mechanisms to flag and classify various levels of errors in ECG XML formatting and provide suggestions on how to fix the discrepancies from the HL7 v.3.0 standard.

The FDAEcg Suite™ represents a clinically relevant innovation by AMPS-LLC that supports the implementation of the FDA digital aECG requirement by pharmaceutical sponsors by enabling the in-house review of digital aECG data from single or multiple clinical trials by digital algorithms and quality metrics for ECG acquisition, processing and interval measurement similar to those used by the FDA during the NDA review. The FDAEcg Suite™ would thus offer pharmaceutical sponsors practical insights into the quality of ECG acquisition by trial sites and the credibility of QT measurement by the central ECG laboratory or the fully automated methods. Sponsor's use of the FDAEcg Suite™ might improve the consistency of digital aECG data quality in preapproval clinical trials, facilitate the submission of digital aECGs to the FDA Warehouse and anticipate the outcome of the FDA review of these ECGs within the NDA. Validation of the utility of the FDAEcg Suite™ in drug development will require the assessment of statistical trends in the scores for quality metrics of digital aECGs from multiple thorough QTc trials and other clinical studies in the FDA Warehouse.

Beyond its use in regulatory approval of new drugs, the FDAEcg Suite™ presents an opportunity to serve as a digital tool for the analysis of large volumes of digital annotated ECG data from clinical trials within the sponsor's in-house repository or at academic research institutions and healthcare organizations. As the functionality of digital algorithms and modules of the FDAEcg Suite™ grows, it could be used to study new biomarkers of proarrhythmia and correlate them with cardiovascular clinical outcomes, potentially facilitating development and therapeutic use of safer medicines.

Product News

Latest Releases

In the last few months the following major updates have been released:

- TrialPerfect v.2: enhanced ECG capabilities, updated exportation.
- HeartScope v2: redesign of the old HeartScope tool for a complete Advanced Analysis of Cardiovascular Signals.

Looking forward

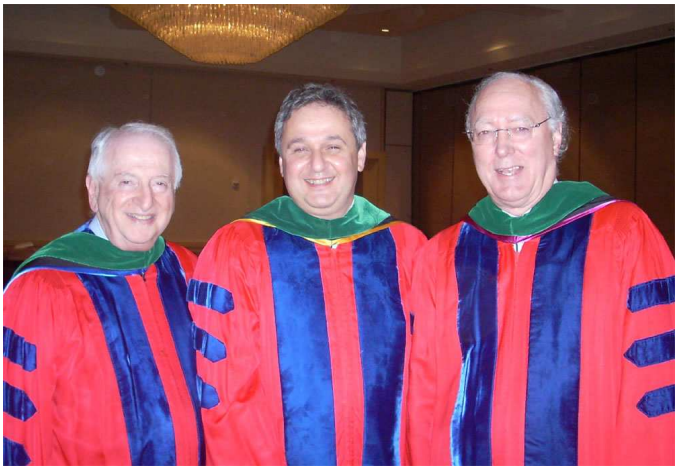
In the next few months, AMPS is planning major releases for the following tools:

- FDAEcg Suite v.2: enhanced graphical interface, with advanced scoring display, new scoring metrics and optimized ECG management.
- Holter Suite: redesign of the old WinAtrec tool with enhanced graphical interface as well as command-line modality for batch analysis, and the Holter analysis, including the famous RR-Bin and Time-Bin methods.
- CalECG v3: totally redesigned graphical interface, updated with new display on ECG signal in predefined format, such as 3 X 4, 6 X 2 and enhanced automatic algorithm for annotation measurements with abnormal beat classification.

A new product will also soon be part of the AMPS portfolio: FAT-QT (Fully Automatic Thorough-QT).
FAT-QT is a fully automated tool that combining features of three of the most successful and confirmed AMPS tools, namely Antares, CalECG and the FDAEcg Suite will provide in one single tool the capability to perform a fully automated analysis from Holter recordings to ECG annotations in matter of seconds. Moreover, analyzing the quality of the ECG waveforms, it will provide a reliability-index of the automatic measurements, thus greatly reducing the need for manual review analysis on a small subset of ECGs.

AMPS Notebook

AMPS was present at the 58th Annual Scientific Session of the American College of Cardiology held in Orlando, FL, where Dr. Fabio Badilini, the founder of AMPS, was honored to receive the 2009 Honorary Fellowship Award.



Dr Fabio Badilini with Prof A.L. Waldo and Prof A.J. Camm at the Honorary Fellowship Award ceremony in Orlando.

AMPS was also present at the DIA Meeting in Bethesda on April 30th and May 1st 2009, where Dr Badilini presented the paper: *"Highly Automated QT Assessment from Holter by Optimized Extraction and Tailored ECG Review"*, which elicited compliments by several stakeholders present at the meeting, including FDA officials. A copy of his presentation can be found on the AMPS web site under the "Useful Documents /Presentations" page in the "Useful Documents/ Publications" section where we offer a list of papers published by the AMPS team.

AMPS people

Lamberto Isola, MS

We continue our round of staff introductions with Lamberto Isola.

Lamberto started his Engineering studies in Italy at the University of Brescia where he obtained his Master Thesis degree in 2006. His graduation thesis was entitled: "*The FDA HL7 XML format, for the representation of annotated digital ECG: analysis and validation and comparison with existing public formats*".
He originally joined AMPS back in 2003, as part-time consultant, while he was still a student. He quickly became interested and proficient in the HL7 XML format to the point of becoming a presenter at the 2nd "*HL7 XML Annotated ECG Workshop*" held in Bergamo, Italy in 2005.
He is currently the leader of the FDAEcg Suite product line and the recognized expert in ECG format conversions and Python scripts for in-house studies management.
He is also in charge of the HS2IHNE converter tool, and is considered by his peers the ultimate authority as far as Mortara H-Scribe and E-Scribe systems are concerned.
His e-mail address is: isola@amps-llc.com