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

As you may remember in the last issue of AMPS-QT (3Q2010) we reported about the release of the RFQ "*ECG WAREHOUSE FOR CONTINUOUS 12-LEAD HOLTER RECORDING*" by the FDA. A few weeks after AMPS-QT was released, it was announced that the project was awarded to Mortara Instrument.

In this last 2010 issue, as a follow up, we are therefore very pleased to welcome an article by Dr. Justin Mortara, PhD, Chief Executive Officer of Mortara Instruments.

For those who don't know Justin, it is maybe interesting to know that he is neither a physician nor an engineer, but rather a physicist, like his father Dave (founder of Mortara Instruments) and not just any physicist!

As it happens, in fact, Justin in 1992 won the LeRoy Apker Award (APS), a prize that has been awarded annually by the American Physical Society since 1978 for "outstanding achievements in physics by undergraduate students" for work he did under Stuart Freedman on the search for a particular type of heavy neutrino. Justin then followed Freedman to UC- Berkeley, entering the physics graduate program in 1992 and earning his PhD in 1999. His doctoral thesis was on the search for violation of the time reversal invariance property of beta decay in Cobalt-56 atoms.

Justin eventually joined Mortara Instrument, worked for nearly a year at the company's office in Bologna, Italy, where he learned to speak Italian, and, after holding different positions, in September 2008 became Chief Executive Officer with responsibility for all executive leadership and associated functional areas.

We could not imagine anybody better suited than Justin to provide this very useful insight to the project, and give indications on how it will likely develop.

As you will see at the end of this issue our team decided to present you its wishes in an original way, so…..

A Noteworthy Contribution:

Extending the ECG Warehouse

By Justin L. Mortara, PhD, Chief Executive Officer; Mortara Instrument, Inc; Milwaukee, WI.

HISTORY OF THE ECG WAREHOUSE

On June 8th, 2004, Mortara Instrument, Inc. announced an agreement with the FDA to collaborate on a digital data warehouse to facilitate review, analysis and archival of cardiac safety data submitted as part of new drug applications. The data warehouse processes electrocardiographic (ECG) data and provides tools for FDA reviewers to manage, review, and analyze submitted HL7 XML datasets more efficiently.
The development effort involved Mortara Instrument engineers in collaboration with FDA's Center for Drug Evaluation and Research (CDER) senior scientists. Development of the ECG data warehouse utilized core technologies from Mortara's E-Scribe Rx ECG data management system as well as new features to facilitate specific FDA submission, review and warehousing requirements. To facilitate regulatory review, the Mortara VERITAS™ ECG algorithms were embedded into the ECG Warehouse to enable automatic analysis of every ECG submitted to the Agency.

The FDA ECG warehouse architecture was designed to be scalable to support the high volume requirements anticipated by the Agency. Today the ECG Warehouse contains over 4 million ECGs, all of which have been automatically analyzed by the VERITAS algorithms. They

represent the largest collection of standardized ECGs in the world.

INFRASTRUCTURE

From its inception, the infrastructure utilized to house, deploy and support the ECG Warehouse has been held to high security and redundancy standards.

The ECG Warehouse has been certified to be in accordance with the requirements of US federal agencies (specifically the US Food and Drug Agency).

The ECG Warehouse servers are hosted in a secure, professionally managed data center that has undergone a SAS 70 Type II audit. SAS 70 is designated by the U.S. Securities and Exchange Commission (SEC) as an acceptable method for a user organization's management to obtain assurance about service organization's internal controls without conducting separate assessments. Additional features of the ECG Warehouse technical infrastructure include:

- Physical security.
- Environmental protection with N+1 redundant HVAC systems and advanced fire suppression.
- Conditioned power with instantaneous failover to uninterrupted power, including on-site diesel generators that can run indefinitely.
- Multiple, independent Internet service providers for uninterrupted Internet service.
- Daily backups with weekly offsite rotation.
- Secure website with 1024-bit SSL server certificate.
- All data encrypted between server and client.
- Secure uploads over encrypted HTTPS. Unique passwords given for each upload.
- Users issued X.509 certificates for identification. More secure than standard "username and password" used by most websites.

The ECG Warehouse support staff has administered the upload of over 400 studies and more than 4,000,000 ECGs. There have been no service outages since the ECG Warehouse started more than 5 years ago. Support staff have also routinely been involved in reviewing annotate ECG file validation reports generated by the ECG Warehouse, coordinating with CROs, ECG central laboratories and sponsors to address non-adherence to the HL7 annotated ECG standard.

HOLTER IN CLINICAL TRIALS

Interest in using Holter in clinical trials surged with the increasing number of study designs requiring significant number of ECG time points to be captured over a short period of time. This so-called "Thorough QT" or "TQT" trial had two basic ECG specific requirements: (a) 12-lead ECG acquisition and (b) frequent ECG time-points over a 24 – 72 hour period.

Traditional Holter, which typically utilized less than 12-lead acquisition, did not meet this requirement. However, in recent years, 12-lead Holter technology has been available, enabling this continuous recording technology to be utilized. The 12-lead Holter approach was validated in an early study using sotalol to prolong the QT interval and compare the measured QT value between a standard 12-lead ECG recorder and that obtained with a 12-lead Holter [1].

One of the early motives for using 12-lead Holter in TQT trials was very pragmatic: the Holter device simply recorded everything and didn't require any human intervention to start a discrete ECG recording. Removing the human intervention achieved two important things: (a) it eliminated the chance that a time point might be missed and (b) it reduced the cost incurred by the Sponsor since the clinical research unit staff didn't have to be used to acquire the ECG.

Of course there are many scientific motives that support the use of continuous recordings [2]. From basic questions like trying to select noise free recording segments to more sophisticated questions around QT/RR dynamicity, QT adaptation and individualized QT corrections – all of these require the use of continuous 12-lead ECG.

THE REGULATORY REQUIREMENT

As previously reported in this newsletter, the US FDA published a Request for Quotation (RFQ) that underlined the need for an expanded ECG Warehouse to support the submission and review of 12-lead continuous data. As stated in the RFQ, "The intent is to support review of continuous recordings that are typically the underlying datasource for the discrete ECGs that are currently being submitted to the FDA ECG Warehouse today. This work will be the first step in positioning the FDA to request the upload of continuous recordings as part of the cardiac safety regulatory review process". Mortara Instrument responded to this RFQ and was awarded the contract to extend the existing ECG Warehouse to support these continuous records [3].

LOOKING AHEAD

We see the development of the FDA Holter Warehouse proceeding along a series of steps over the next year.

Initial steps will include formalization of standards based approach to submission of continuous data, creation of new data transfer models for moving larger volumes of ECG data, automatic processing of continuous data using the Mortara VERITAS analysis engine and refinement of U/I behaviour based on collaboration with FDA personnel.
We look forward to keeping all interested parties engaged, especially in discussions around standards extensions or enhancements as required. When we built the FDA ECG Warehouse, we prepared for, but had no idea that more than 4,000,000 ECGs would come! So when we complete the Holter Warehouse, how many will arrive?

We will be sure to let you know.

REFERENCE

[1] Sarapa, N., Morganroth, J., Couderc, J.-P., Francom, S. F., Darpo, B., Fleishaker, J. C., McEnroe, J. D., Chen, W. T., Zareba, W. and Moss, A. J. (2004), Electrocardiographic Identification of Drug-Induced QT Prolongation: Assessment by Different Recording and Measurement Methods. Annals of Noninvasive Electrocardiology, 9: 48–57.

[2] It should be noted that Holter is one means of collecting 12-lead continuous recordings, but it is also possible to collect the equivalent 12-lead continuous recordings via telemetry as well.

[3] An announcement of the contract award is available at http://www.mortara.com/news-events/news/detail/mortara-instrument-announces-extension-of-ecg-warehouse-crada-with-us-fda-2/

AMPS Notebook

Fabio Badilini was present at the annual CSRC meeting held at the FDA in Washington DC, December 8th – 9th.

Best Wishes for Happy Holidays and all the best for 2011 from the AMPS Team!