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

Summer is barely over and 2010 already promises to be one of those years people will always remember. The first half of the year was indeed already so packed with events and exciting news concerning our industry, making several people pause and think: "now what?", that the timing of the release of the RFQ "*ECG WAREHOUSE FOR CONTINUOUS 12-LEAD HOLTER RECORDING*" by the FDA at the end of July, its relevance, and the changes it may entail in the long run, might have eluded some of our readers.

The FDA ECG Warehouse has been in operation now for 5 years, it contains to date approximately 3.8 million ECGs and has enabled FDA on-line review of over 100 TQT trials. What has happened since the inception of the warehouse, and we at AMPS are partly responsible for it, is that more and more of the submitted 12-leads, 10-seconds ECGs are actually obtained from day-long recordings, aka Holters, either through automated extractor tools, such as our own well know, and widely used, Antares, or by manual selection. Several stakeholders in fact found it more safe, reliable, and ultimately convenient, to collect and analyze Holter recordings in the context of TQT trials rather than traditional 10-seconds ECGs. Up to now however the FDA only requested, and accepted, 10-seconds resting ECGs, thus the need for extraction.

The FDA, well aware of the growing phenomenon, clarified its view in the RFQ, stating that: *"This is unsatisfactory for several reasons. First, the process for selection is not subject to audit. Second, the time points may not be adequate to discriminate real signals from random variation. Third, there is inherently more information in the recordings than can be captured in 10-second snapshots. Fourth, there are other settings in which the review of continuous ECG data would be invaluable, for example, in the assessment of new antiarrhythmic therapy",* and it therefore decided to create an ECG Warehouse to support inclusion of continuous ECG recordings in addition to the existing discrete recording support. As specified in the RFQ: *"The intent is to support review of continuous recordings that are typically the underlying data source 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".*

We salute this decision by the FDA as a major step forward for cardiac safety and we believe this may represent the first, small but important, step to encourage the industry toward a shift from the usage of the classic 10-seconds ECG traces towards the usage of continuous ECG recordings for TQT trials in the future. This initiative now also generates the need to define and select an open standard format for Holter recordings, as it was the case for the ECGs at the beginning of the original Warehouse project, which ultimately lead to the development of the HL7 xml standard. The RFQ in fact also specifies that: *"The enhanced ECG warehouse shall support the existing HL7 format for digital ECGs of arbitrary length. In addition, the contractor shall support an alternative open standard for long digital ECGs, to be selected in conjunction with the FDA PI".*

Given Dr. Badilini's key role in the definition of the HL7 xml format and the AMPS track-record in providing reliable format-conversion tools both for resting ECG formats and for Holter formats, we are looking forward to participate in the open process for the definition of the new standard and we promise to keep our readers updated on the progress.

The RFQ, as it often happens, generated a flurry of activity, by various stakeholders, to respond in time for the deadline, which was eventually extended to August 17th. In fact, by its own admission: *"The Government knows of only one source, Mortara Instrument, Inc., that is capable of performing the services described in this combined synopsis solicitation. However, in attempts to search the market for capabilities of other companies, FDA has determined full and open competition to be in the best interests of the Government".*

As of the date of this article, and to the best of our knowledge, the FDA has not announced yet to which company the project will be awarded, but if there is someone, beside Mortara Instruments, with a good background knowledge about a Holter warehouse clearly that is the non-profit THEW organization, hosted at the University of Rochester. We welcome in this issue an article by the THEW Director, Dr. Jean-Philippe Couderc, which will help our readers to gain a better understanding on how the new FDA Warehouse may end up looking like. Enjoy!

A Noteworthy Contribution:

The Telemetric and Holter ECG Warehouse Initiative (THEW): a Data Repository for the Design, Implementation and Validation of ECG-related Technologies

By Jean-Philippe Couderc, PhD, MBA ; Heart-Research Follow-Up Program, Rochester, NY.

INTRODUCTION

Cardiac safety remains a major public health concern. Sudden cardiac death (SCD) is responsible for half of all heart disease deaths and is the largest cause of natural death in the U.S. (representing about 325,000 adults each year in the US). Despite the effort implemented to reduce this number by early advanced care, there is a clear need for the improvement of risk stratification techniques to optimize the use of prophylactic therapies such as implantable defibrillators and drug therapies. Meanwhile, cardiac safety is also one of the most challenging hurdles in the development of new molecular entities. It has been estimated that as many as 86% of all drugs tested in pharmaceutical development show specific inhibitory activity of potassium ion kinetics, which in some cases can lead to 'Torsades de pointes' and subsequently to sudden cardiac death.

The National Heart, Lung and Blood Institute (NHLBI) provided the resources to University of Rochester (NY) to enable the creation of the "Center for Quantitative Electrocardiography and Cardiac Safety" (CES). These resources support the inceptive CES activities around 1) the development and maintenance of computer resources (data storage and computing center), 2) the deployment of medical information, and 3) the formation of a scientific network. The CES distributes these resources to the international scientific community by sharing unique clinical and ECG information for the design and validation of technologies to improve quantitative electrocardiography and cardiac safety.

In addition, the CES developed a partnership with the U.S. Food and Drug Administration (through a FDA private-public partnership - PPP). Under its public health mission, FDA is interested in the development of improved technologies to evaluate drug safety and efficacy [1]. This FDA partnership was designed to leverage resources and expertise toward the implementation of collaborative projects among FDA, University of Rochester and other public and private stakeholders. Out of this collaborative effort, specific projects were started to expand the data in the CES repository (THEW), and facilitate scientific projects toward the development, testing and and validation of ECG-related technologies.

THE THEW INITIATIVE

Mission Statement

The objective of the Center for Quantitative Electrocardiography and Cardiac Safety and its Telemetric and Holter ECG Warehouse (THEW) is to provide access to electrocardiographic data to research organizations for the design and validation of analytic methods to advance the field of quantitative electrocardiography with a strong focus on cardiac safety. [2]

Information Technologies Infrastructures

The ECG recordings from the warehouse are currently hosted in two servers: 1) a SFTP server located at University of Buffalo (NY) and 2) a client-based access server located at University of Rochester Medical Center (NY).

Our resources include an IBM BlueGene/P super computer as well. This system consists of one rack of the 13.9 TFLOPS IBM Blue Gene/P massively parallel processing (MPP) supercomputer, one IBM System p front-end node, one IBM System p service node, and 8 IBM System x I/O nodes connected to 180 TB IBM System Storage. The Blue Gene/P system consists of 1,024 nodes, 4,096 CPU cores, 2 TB of RAM, and 180 TB of storage. Each node consists of a quad-core PPC450 with 8 MB of cached and 2 GB of RAM. Access to this computer resource to THEW users is currently in development.

WAREHOUSE CONTENT

ECG recordings

The data available in the warehouse were provided by research academic centers and major pharmaceutical companies. The current list of database is provided in Table 1. The hosted ECG recordings are continuous with a length varying from 10 minutes to 24 hours. The equipments used to record the ECGs differ between databases, thus the technical specifications of the recordings are different between databases.

The ECG signals can have a sampling frequency of 180Hz, 200Hz and 1000 Hz and an amplitude resolution coded on 10 to 16 bits. The lead configuration depends on the recording equipment as well. Currently, the datasets contain either 2, 3, 8 or 12 lead recordings. Three leads recordings are recorded using a pseudo-orthogonal configuration (X, Y, and Z). Twelve leads followed Holter configuration in which limb leads are reported to the torso (Mason-Likar lead placement) and the precordial leads follow the standard resting 12-lead ECG configuration.

Database links	Leads	Sampling	ECGs	Ind.	Size
Healthy individuals	3	200 Hz	201	201	22 GB
CAD patients	3	200 Hz	271	271	29 GB
AMI patients	3	200 Hz	160	93	18 GB
Thorough QT study #1	3	200 Hz	175	34	6 GB
TdPs recordings	12	180 Hz	6	6	2 GB
Pts with history of TdPs	12	1,000 Hz	68	34	242 MB
AFib. patients	12	1,000 Hz	73	73	1.7 GB
Thorough QT study #2	12	1,000 Hz	140	70	190 GB
Chest Pain Patients	12	180 Hz	1172	1154	336 GB
Genotyped Cong. LQTS	2 or 3	200Hz	480	307	14 GB
TOTAL			2,762	2,146	619 GB

Table 1: Datasets currently hosted in the THEW
CAD: coronary artery disease; AMI: acute myocardial infarction; TdPs: torsades de points; Pts: patients; Afib: atrial fibrillation; LQTS: long QT syndrome

Study populations in the repository

The THEW databases encompass ECG recordings from cardiac patients and healthy individuals. As described in Table 1, 24-hour continuous Holter ECGs from patients with acute myocardial infarction (AMI), patients with coronary artery disease (CAD), 10-minutes continuous ECGs from patients before after cardioversion for atrial fibrillation (Afib) and finally patients with the congenital or the acquired long QT syndrome are included. Several of them contain documented life-threatening ventricular arrhythmias (torsades de pointes).
Long term continuous Holter ECG from healthy individuals are available including individuals exposed to drugs such as moxifloxacin in the thorough QT studies.

ECG and annotation file formats

The database-specific technical specifications of the data are supported by the ECG file format used in the warehouse namely the ISHNE Holter ECG format [3], a hybrid version of this format was developed by AMPS LLC (New-York, USA) to host the information related to cardiac beat annotation. This format is described as follow:

1. ISHNE header as described in [3]
2. Binary annotation consisting of a 4-bytes binary data structure organized as follows:
    - Label 1 [char]: beat annotation
    - Label 2 [char]: for further beat description
    - location (Δ Sample): digital samples from last beat annotation [unsigned int]

The definition of the label is as follow for label 1:
N: Normal beat
V: Premature ventricular contraction
S: Supraventricular premature or ectopic beat
C: Calibration Pulse
B: Bundle branch block beat
P: Pace
X: Artefact

Clinical information

As noted above, the THEW consists of ECG recordings from cardiac patients, healthy individuals, individual exposed to cardiac and to non-cardiac drugs. The clinical information associated to these populations are heterogeneous. Consequently, we opted to release dataset-specific files for describing clinical information (including medical history, study endpoints, etc.). These clinical files are provided in either MS Excel or SAS format. The list and the number of clinical variables vary between databases, a description of the database-specific set of information is provided in our website. Importantly, none of the clinical information available in the THEW contains health private information and all available information are fully compliant with HIPAA regulation.

The THEW Client Application (CA)

The THEW CA is a Microsoft dotNET (framework 2.0) application developed in collaboration with Global Instrumentations (Syracuse, NY). This application is designed to provide: 1) easy secured access to ECG and clinical data, 2) ECG viewer tools, 3) ECG tools for interval (epochs) extraction from Holter recordings, and 4) a system development kit based on a simple application program interface (API). To obtain the latest version of the software, the users can send a request using the download area of our website (see Web links at the end of the article).

The epoch selection tool allows for identifying intervals of interest from the continuous ECG recordings. Once the epoch is defined, the CA provides an interface to download the period of interest so the users do not have to download large amount of signals (when it is not needed). The download tools of the CA provide several extraction formats such as ISHNE, HL7 aECG and ASCII files with self-explanatory configuration.
To simplify the users' access to relevant epochs of recordings, we predefined sets of epochs in each ECG recordings. For example, in our set of ECGs including

drug-induced torsades de pointes, we created epochs covering a period preceding the occurrence of the arrhythmias.

The secured FTP server

The user of the THEW data have the option to access the data from the warehouse using a secured FTP server hosted at University of Buffalo with the support from the NYSTAR program (New-York State Foundation for Science, Technology and Innovation). The server is hosted at the Center for Computational Research New York State Center of Excellence in Bioinformatics & Life Sciences. The data in the server are in ISHNE format including both the raw ECG signals and the annotation information.

Legal use of the data from the THEW

The data from the THEW can be used for research, development and educational purposes. No restriction exists related to publications, inventions and patents i.e. intellectual properties based on the THEW data is fully own by the inventor and cannot be claimed by either the THEW organization or the organization(s) that provided the data to the THEW.

Importantly, the data from the THEW cannot be shared between organizations without prior consent from the THEW organization (regardless of their status). Such requirement is necessary in order to have for-profit companies helping us continuing to develop our activities through membership data-access fees. Thus, we ask any THEW users to sign a Data Use Agreement (DUA). As today, this agreement was executed by more than 20 organizations worldwide. In the following section, we describe how AMPS became one of the first company to join our initiative.

A successful academic and private collaboration: AMPS and the Telemetric and Holter ECG initiative

Very early AMPS expressed an interest in the THEW initiative, and this organization became one of the first "Founding Fathers". Noteworthily, AMPS was one of the first companies to sign the THEW technology sharing agreement. The agreement provided the software suite of ECG conversion tools to the THEW from AMPS and in exchange AMPS gained THEW membership with full access of the data in the repository. The conversion tools were and remain used today for converting ECG recordings in ISHNE format to be inserted in purr repository.

For instance, AMPS technology enabled the integration of the dataset of high-resolution Holter ECGs from a thorough QT studies conducted and shared by Hoffman-Laroche (Palo Alto, CA). Hundred and forty 24-hour Holter recorded using the H12+ recorders from Mortara Instrument (Milwaukee, MN) are included. Hosting this data in our repository required the proprietary format of these ECGs to be converted in ISHNE format, in order to be shared openly with the worldwide scientific community.

Another database that benefited from AMPS tools was added to theTHEW this year. It is the French registry of patients with the inherited long QT syndrome. A set of 480 24-hour Holter recordings from genotyped patients with this syndrome were acquired in Paris hospital (Lariboisiere) over more than a decade. Fabrice Extramiana and his group agreed on sharing these recordings with the scientific community through the THEW. AMPS and Lariboisiere ensured data de-identification and data conversion and send us the ECG recordings readily formatted for integration into the THEW. Importantly, this database includes information about gene mutation and their location, the availability of both ECG recordings and identified gene mutations is a unique feature that has never been gathered and shared openly in a digital repository.

Finally, AMPS technology was at the heart of our chest pain database: a dataset of 1,172 recordings entirely converted into ISHNE format using the AMPS tools. The processes included both low-resolution (180 Hz) and high-resolution recordings (1000 Hz). The high-resolution recordings are scheduled for released before the end of the year.

CONCLUSION

In conclusion, an increasing number of companies have realized that collaborative arrangement with our non-for-profit organization (THEW) provides an opportunity to contribute toward a relevant purpose different from profit maximization. Large pharmaceutical companies have shared their data other their technologies such as AMPS. These organizations have benefited from these agreements, and their efforts have not been driven primarily by monetary reward but rather the ability to grow an initiative that benefits the scientific community and the society through combined efforts.

USEFUL LINKS RELATED TO THIS ARTICLE:

- THEW website: http://www.thew-project.org
- NYSTAR website: http://www.nystar.state.ny.us/
- Center of Excellence in Bioinformatics & Life Sciences: http://www.bioinformatics.buffalo.edu/

- FDA Private Public Partnership website: http://www.fda.gov/AboutFDA/PartnershipsCollaborations/PublicPrivatePartnershipProgram/ucm166082.htm
- Center for Research Computing website: http://www.rochester.edu/its/web/wiki/crc/
- HL7 aECG format: http://www.hl7.org/V3AnnECG/

REFERENCES

[1] FDA, "Innovation, Stagnation. challenge and Opportunity on the Critical Path to New Medical Products," US Department of Health and Human Services Food and Drug Administration,2004.

[2] Couderc JP. A scientific repository to support the research and development of technologies related to quantitative electrocardiography: the Telemetric and Holter ECG Warehouse (THEW). Cardiol J. 2010;17(4):416-9.

[3] F. Badilini, "The ISHNE Holter standard output format," Ann. Noninvasive. Electrocardiol., vol. 3, no. 3, pp. 263-266, 1998.

Products News

Latest Releases

Last month TrialPerfect version 2.6.0 was released. This new version supports and integrates the automatic interpretations generated both by the Glasgow algorithm, imbedded in CalECGv3, and by Fat-QT, allowing an automatic ECG reading and classification.

Looking forward

In the fall 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 was at the 37th Computing in Cardiology Conference held in Belfast, Ireland September 26th – 29th. Fabio Badilini and Martino Vaglio presented 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 Giuseppe Corbelli.

Giuseppe started his Engineering studies in Italy at the University of Brescia where he obtained his Master Thesis degree in 2005. His graduation thesis was entitled: *"Project of a software instrument for reproducibility analysis in the Pharmaceutical area"*.

Giuseppe, who joined AMPS in 2004, is an expert in operating systems and C++/Python languages; he is also the AMPS system administrator. His e-mail address is: corbelli@amps-llc.com.