



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

Welcome to the first issue of AMPS-QT, the AMPS Quarterly Journal. We wish to clarify from the very beginning that the main purpose of AMPS-QT is not to become yet another scientific journal, competing with all the already existing authoritative publications in the field of cardiac safety. With this publication we begin what we expect is rather going to be an interesting and successful series of articles contributed by key people and influential stakeholders, active in the field of clinical trials and TQT studies and willing to share their views and ideas. AMPS-QT also wish to become a useful communication tool for all existing and future AMPS customers and a mean for them to learn regularly about the new methods and tools developed and released by AMPS. Contributions and ideas for articles as well as comments are welcome. Please send them to: AMPS-QT@amps-llc.com.

AMPS Views on:

Continuous Holter in clinical trials

Usage of continuous Holter recording as the primary mainframe of data support in pharmaceutical clinical trials is a matter of debate. One reason for concern is certainly the technical performance of recording devices which still cannot fully match the specifications of standard ECG carts. But the big question remains how the huge amount of recorded data, namely the roughly 100,000 cardiac beats available in a 24 hour time window should be managed and processed. As of today, regulatory organizations have not issued specific documents on how continuous data should be used, and Holter is mainly used in phase I and in Thorough QT studies as a practical support for off-line extractions of 10 second ECGs.

Despite this, techniques which take into account the true essence of Holter are being developed and finalized. Methods that have already been occasionally employed in clinical trials (as part of secondary endpoint) are either based on beat-to-beat or on averaging techniques. In the latter group is the so-called Holter bin, a method that was introduced by AMPS. It became known to pharmaceutical world with the Alfuzozin study.

On Holter-bin methods. AMPS Holter-bin is a spin-off of a research package developed in the late 1990s at the Lariboisiere Hospital in Paris, the group that introduced a method to characterize the repolarization substrate in LQTS populations. The method has been used in numerous publications and is today a standard to assess quantitative ECG analysis with or without changes in the heart rate. For more information refer to “QT interval analysis on ambulatory electrocardiogram recordings: A selective beat averaging approach” and “Contrasting Time and Rate based approaches for the assessment of drug-induced QT changes” papers from the Publications page available on our Web Site.

With AMPS Holter-bin, beat waveforms preceded by the same heart rate are averaged with complex signal processing techniques that take into account the characteristics (resolution) of Holter recordings. For each heart rate (RR bin), a representative waveform is thus considered and analyzed. The “within bin variability” is assessed providing distribution information of the individual beats used to obtain the representative waveform (for example noise).

Alternative techniques that use the same concept with some variants have recently been introduced. In one specific example, instead of averaging individual beats, the single beat-to-beat measurements (such as QT intervals) are pooled together. In this case the “within bin variability” is assessed providing distributions of the single beat measurements (for example means and SDs of QT intervals).

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Despite a few marketing statements on the superiority of one of these methods, a scientific comparison based on the same set of data has never been done and thus any related claim would be purely speculative. While each of these techniques can well suit the needs of basic science, their accuracy to properly detect drug-induced changes should be established on a case-by-case scenario. AMPS Holter-bin has been extensively used in many pharmaceutical trials, including several thorough QT studies, three of which are ongoing in compounds that modify the heart rate.

On hysteresis. Continuously acquired ECG data provides the optimal background to properly cope with the confounding effect of hysteresis. As of today, two distinct approaches have been proposed: in the first a hysteresis-corrected heart rate is determined for each beat; in the second only the ECG portions preceded by stable heart rate (i.e. those where hysteresis is not present) are considered. The advantage of the first approach is that all the data can be used for analysis (although somewhat more complex) whereas the second is much simpler and safer to implement (with considered unstable data however discarded). Some methods are considered better than others for handling hysteresis. This is a misconception since all Holter-based techniques can take hysteresis into account applying either one of the two approaches mentioned above.

Conclusions. While waiting for clear guidelines from regulatory organizations, methods based on continuous ECG data are likely to be used as secondary endpoint approaches, typically employed for compounds associated with significant heart rate changes. In addition to Holter-bin, AMPS also offers other solutions, including beat-to-beat analysis, time-based binning, and several beyond QT (HRV, morphological analysis) techniques.

The AMPS mission is to keep the focus on current and new methodologies, always in close collaboration with regulatory agencies, and thus continuing to provide state of the art technology to customers.

Product News

AMPS LLC has released a new and improved XML Viewer Light.

Over one year ago AMPS announced the sunset of the well known XMLFDA Viewer product and the release of the AMPS FDAECG Suite, the modular AMPS solution for HL7 xml format ECGs. It includes an extensive set of qualitative and quantitative tools ranging from ECG quality

scoring to HL7 XML validation at different level. The success of the AMPS FDAECG Suite proved that, beyond increased functionality, the new graphical interface and redesigned menus have struck a responsive chord.

AMPS LLC is now pleased to announce the release of the AMPS Viewer Light. This new product replaces the old XMLFDA Viewer Light and provides the much improved graphical interface of the AMPS FDAECG Suite, as it is based on the same code. Similarly to the old Light product the new AMPS Viewer Light provides a way of displaying and validating one HL7 xml ECG file at a time. Over the last few years, the XMLFDA Viewer Light has been widely adopted by the healthcare industry, ranging from pharmaceutical companies, Core labs, and private clinical practices. The new AMPS Viewer Light can be licensed from AMPS, like its predecessor, via a one-time charge. AMPS customers already owning a license for the XMLFDA Viewer light will be able to upgrade to the new product at a discounted fee.

Looking ahead

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

- o TrialPerfect v.2: enhanced ECG capabilities, updated exportation.
- o FDAECG Suite v.2: enhanced graphical interface, with advanced scoring display, new scoring metrics and optimized ECG management.
- o 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.
- o HeartScope v2: redesign of the old HeartScope tool for a complete Advanced Analysis of Cardiovascular Signals.

AMPS Agenda

AMPS participated in the Computers in Cardiology Conference in 2008 held in Bologna, Italy, September 14th to 17th. The meeting provided an international forum for scientific presentations focusing on computer applications in clinical cardiology and cardiovascular research. The Conference web-site is: cinc.org.

We were also present at the 3rd European DIA Meeting Cardiac Safety Conference, held in Barcelona, Spain on December 4th and 5th, 2008. Here Fabio Badilini actively participated with the following presentation: "Optimized

ECG Extraction from digital 12-lead Holter based on noise and heart rate criteria”.

AMPS will be present at the 58th Annual Scientific Session of the American College of Cardiology held in Orlando, FL, where Fabio Badilini, the founder of AMPS, will be honored to receive the 2009 Honorary Fellowship Award. Refer to the AMPS people section for more details.

AMPS people



Fabio Badilini Ph.d

In each issue of AMPS-QT we will focus on a member of the AMPS Staff.

As this is the first issue, we are focusing on the AMPS founder, Executive VP and Chief Scientist, Fabio Badilini.

Fabio started his Engineering studies in Italy at the Polytechnic of Milan where he obtained his doctoral degree in 1989, focusing, already back then, on “Beat-to-Beat Variability of the Cardiovascular System”.

He then continued his studies at the University of Rochester, NY, obtaining an M.S. and a PhD title in 1991 and 1994 respectively. Here he focused on “Time and Frequency Analysis of ST Segment” with the supervision of Edward Prof. L Titlebaum and Prof. Arthur J Moss.

He then moved back to Europe, spending four years in Paris at Lariboisière Hospital with Prof. P Coumel.

Finally in 2001 he founded AMPS.

Badilini is the author or co-author of numerous publications in computational science and engineering, numerical analysis, and computer science applied to cardiovascular signals.

Awards

October 2 2003: FDA Commissioner Special citation for “Development of a format for regulatory submission of annotated electrocardiographic waveform data to meet FDA needs in assessing the proarrhythmic potentials of drugs”.

Fabio Badilini has been selected by the Awards Committee and Board of Trustees of the American College of Cardiology to receive the 2009 Honorary Fellowship Award in recognition of his contributions to the field of non-invasive electrocardiology.

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