

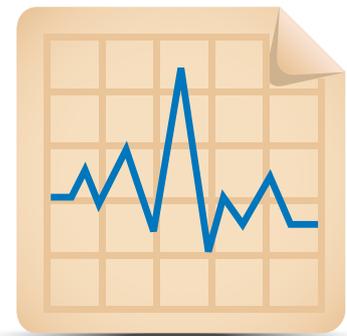
## The thorough approach to QTc studies ECG Data Management

Testing the effects on the QT/QTc interval, and hence cardiac re-polarization, is an integral part of the clinical development of new agents such as non-antiarrhythmic drugs, and recommendations on the design, conduct, analysis and interpretation is provided by the ICH Harmonised Tripartite Guideline E14. ECG reading by machine has an important role in the rapid assessment of ECGs for safety.

Richmond Pharmacology has extensive experience in the conduct of intensive thorough QTc studies. We are proud to offer a dedicated, highly skilled team within an efficient and safe hospital environment, using state of the art technology.

### The Challenge

Depending on the study design and the number of subjects, the volume of ECGs could easily add up to 15,000-30,000 per study, The ECGs must be timely processed with accuracy, precision and with consistent high quality. The pitfalls could be many and it is of the utmost importance to design the study, processes and procedures in an optimal way.



#### Comment

“Our unique collaboration with the renowned Department of Cardiac and Vascular Sciences at St George’s University of London, provides access to world leading Cardiologist Professor AJ Camm and his colleagues for your optimal thorough QTc study.”

### How do we do it?

In short, by digitally recorded electrocardiograms: 10-second simultaneous 12-lead ECGs in triplicate. Measurement of the QT interval is performed automatically with subsequent manual on-screen over-reading using electronic callipers by cardiologists with extensive experience with manual QT measurement (including on-screen measurement with electronic callipers) from the Department of Cardiac and Vascular Sciences at St. George’s University of London

In more detail, the cornerstones that make our approach unique are the tools, the design, the semi-automated process and the experienced ECG team.

## The platform

All of the beds in our wards are equipped with a MAC1200 ECG machine, which provides state of the art technology. All machines are connected to a network with a Muse system on a server. The system is FDA 21 CFR 11 compliant with authorized user access, secure and password protected on different user levels. A complete and full audit trail is available and includes username, date and time of any addition or change made to the database.

### Comment

“In a traditional setting a high volume of paper ECGs are produced and a manual time-consuming process applied with several potential sources of error. The solution Richmond offers minimizes the risk of potential errors and bias. One of several advantages is there is no need for the study team to go to each bed and read a paper ECG. All information is available on screen from one central PC.”

## Standardisation



ICH E14 stresses the importance to ensure consistency of operator technique, e.g. skin preparation, lead placement, subject position etc. At Richmond these steps are all part of our standard process.

Prior to commencement of the study, all ECG machines used for the project are configured to ensure that every ECG data file contains the exact and correct information in a standardised format as per client and protocol requirements. The configuration of an ECG machine is validated which includes acquisition and transfer of test ECGs from the machine's simulator. To further standardise the process, the same machine is always used for the same subject throughout the study. The entire configuration and validation process is fully documented.

In addition the ward is prepared to provide a quiet environment with no interference from external sources.

## Blinding

In accordance with ICH E14, readings are blinded to time as individual QT interval differs between mornings and evenings. In addition, information such as study period, study day, and gender (females usually have longer intervals) is blinded to the reader.

#### Comment

“The standardisation of procedures and blinding of subject details during evaluation are techniques used to ensure a high validity of a clinical study and its results. At RPL we pay pride in applying the most rigorous steps to minimize the influence of any bias.”

## The Quality

During the study, Richmond Pharmacology’s ECG data management team tracks all the acquired ECGs and applies stringent quality control checks to ensure that all planned and unscheduled ECGs are accounted for, and that the time points, subjects’ identifiers and demographic data are properly recorded. This process is done on an ongoing basis during the clinical conduct of the study which allows for the clean ECG data to be available for the analysis almost immediately as the last subject completes the trial.

#### Comment

“An on-going reconciliation of data against the clinical database / CRF is a pro-active quality check that allows timely access of clean data immediately after study end.”

## The process

Richmond can provide a fully manual or a fully automated review according to sponsor’s requirement. However, we believe a semi-automated process is the most efficient. The method is regulatory compliant and each ECG reading is assessed for accuracy by an experienced and fully trained cardiologist.

If the cardiologist is satisfied with the automatic reading, no further action is taken. In the case the cardiologist is not in agreement with the automated reading, the ECG is sent to a second cardiologist for a re-assessment. If in agreement with the first reader, agreement defined as 4.0 msec, no further action is taken. If the difference between the two assessments is >4.0 msec, the ECG is subject to a final review by Professor AJ Camm.

To measure a QT interval is actually relatively easy, and in approximately 80% of the cases the machine reads perfect. Sometimes however, it gets confused by the morphology as morphological changes in the T-U complex might occur. To adjust for the possible effect of the morphology on the reading, an eCRF is used by the cardiologist completing of a number of questions. This is done by a so called split-screen technique, i.e. the ECG is displayed on-screen together with the eCRF.

All QC checks and any corrective actions are reconciled and fully documented.

In line with the current regulatory requirements and at least every six months, all cardiologists undertake intra- and inter-reader variability tests under blinded conditions to ensure that our measurements are as accurate and reproducible as possible.



Finally, the measured and verified QT intervals are corrected for heart rate using conventional population-derived formulae (e.g. Bazett, Fridericia) or an individually derived formula– or both. The QT/QTc interval data are then subject to a statistical analysis in accordance with the ICH E14 guidelines. Experienced cardiological scientists will provide input to the analysis and the interpretation of the results.

We will present your data and results of the QTc analysis effectively and in a timely manner both as a ‘stand-alone’ report and incorporated in the integrated study report, as required. These reports are written by our professional, full time, in-house medical writers with senior cardiologist review and input.

#### Comment

“Richmond’s unique approach to the conduct of QTc studies, with in-house expertise and vast experience makes us your perfect partner for conducting definitive thorough QT studies, all under one roof.”

**We know we can help your business. We always rise to the challenge click here to challenge us.**