

## **Establishing Metrics for ECG Recording Quality: The Role of the ECG Warehouse**

*Cardiac safety management has undergone a major evolution in the last few years. Philippe L'Hostis explains how new developments are of key importance to those managing ECG-related contracts with CROs.*

### **Introduction**

The most significant changes in cardiac safety management relate to regulatory requirements (ICH E14 guideline) and to the collection, storage and analysis of electrocardiographical data. The resulting increase in prerequisites for technical and data submission has played an important role in the creation of dedicated Core Labs working to implement reliable processes for ECG collection and analysis.

Alongside this, global ECG Warehouses have been set up, allowing ECG data to be managed digitally. As a result, it is now possible to set up and use objective criteria (metrics) for consistent quality management within clinical trials.

### **Why is Good ECG Data so Important?**

Cardiac tolerance is a deciding factor in drug development. The quality of ECG data is therefore extremely important, particularly in relation to the QT interval (a biomarker for cardiac repolarisation) and Thorough QT Studies (a regulatory study, defined in the ICH E14 guideline, to evaluate the cardiac safety of a compound by using the QT interval as a biomarker for potential issues).

### **ECG Data Collection & Storage**

Data (waveform & annotations) for each particular study is sent to a global ECG warehouse. Though the ECG Warehouse idea was originally for data submission purposes, the information can be used more widely.

It is, for example, possible to use this structured data to implement a computerised evaluation of the ECG signal quality, and to then derive appropriate metrics.

### **Who is Responsible for ECG Quality?**

Within a study, global performance regarding the quality of ECG data relies upon the performance of both the clinical site and the ECG Core Lab.

The clinical site is in charge of the volunteer recruitment, hospitalisation and practical implementation of the protocol. The ECG Core Lab oversees the study set-up and trains the site staff to ensure the proper use of the ECG devices.

After this training it is the responsibility of the site to record good ECG. To do this, they must follow rigid guidelines in every aspect including volunteer preparation, electrode positioning, and rest periods. The ECG Core Lab should then proactively monitor the quality of the data collected and decide on any appropriate corrective actions.

To ensure good quality data, good communication between clinical sites and Core Labs is essential. For maximum efficiency, the results should be made available online so that clinical site staff can make immediate changes to their practice if necessary.

## The Consequence of Poor Quality ECGs on QT Interval Measurement

Figs. 1 and 2 show how a poor quality ECG can jeopardise the reliability of QT interval measurements.

Fig 1: A good quality ECG

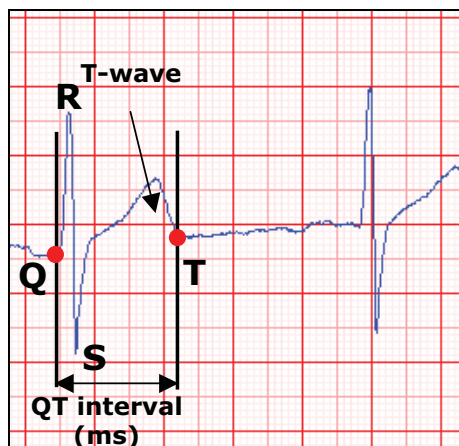


Fig. 2: A poor quality ECG

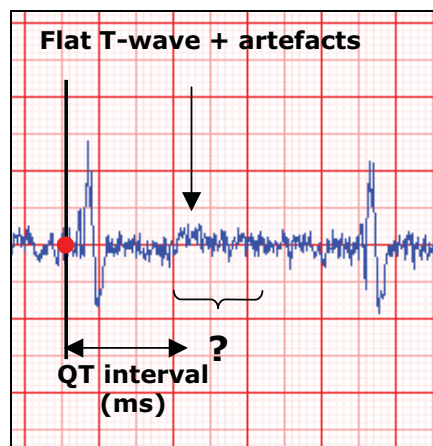


Fig. 1 shows a good quality ECG. The amplitude of the T-wave is of sufficient size to enable a reliable determination of the end of the T-wave. In comparison to Fig 1, Fig. 2 shows a poor quality ECG. There are artefacts in the recording and the T-wave is flat. This is probably due to inadequate skin preparation. In this case it is very difficult for a cardiologist to define the T-wave offset precisely; as a consequence the QT interval measurement can be out as much as 100 ms.

## How High QT Variability can “Kill” the Compound

To illustrate the consequences of this type of imprecision, let us have a look at a Thorough QT/QTc study. To be considered as negative (no effect of the compound on the QT interval), the study must prove that the compound does not induce an increase of the QT interval of more than 10ms (as a mean value). The greater the variability of the QT measurement, the higher the likelihood that the study will be positive and any further development of the compound blocked. As we have seen above, great variability can be caused by poor quality ECG data. Poor data can therefore cause potentially promising compounds to be blocked unnecessarily.

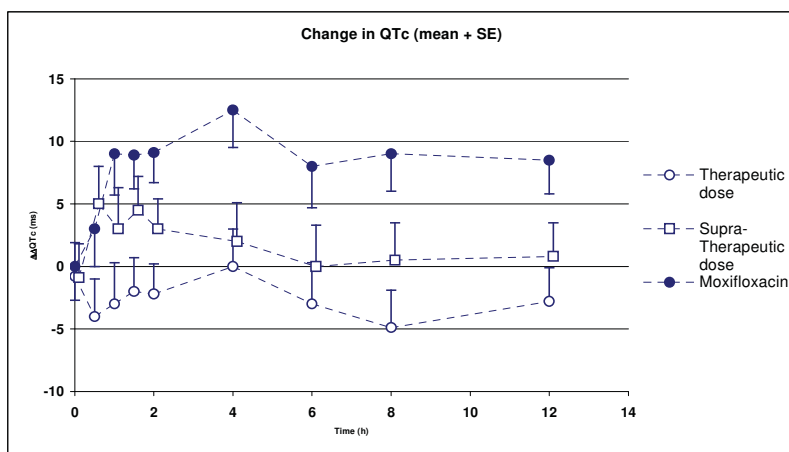


Fig.3

At time point 0.5 hours for the supratherapeutic dose, the upper limit of the confidence interval is below the 10ms threshold. In the case of a high QT variability measurement inducing a wider confidence interval, this upper limit could be higher than 10ms.

The QT/QTc study would be considered as positive.

The immediate reaction to such issues of variability is often to increase the power of the study by including more subjects. Whilst this may make it possible to draw more reliable conclusions, larger studies inevitably cost more. The implementation of a quality metric within the ECG Warehouse will reduce variability and increase the power of the study without the same effect on costs.

### Quality Score Definition & Usage

Every ECG saved in the ECG Warehouse is automatically evaluated against a multitude of factors including:

- Noise level (low/high frequency)
- Baseline stability
- Electrode placement
- T-wave amplitude

The score is synthesised from all these factors. The higher the score, the lower the quality of the ECG recording.

Fig.4 below shows how regular evaluations can ensure that overall ECG quality at each site remains acceptable throughout a long duration study.

Figs. 5 and 6 then show how score values can be compared between sites. This provides an objective assessment useful after the study for ranking vendors and making future outsourcing decisions.

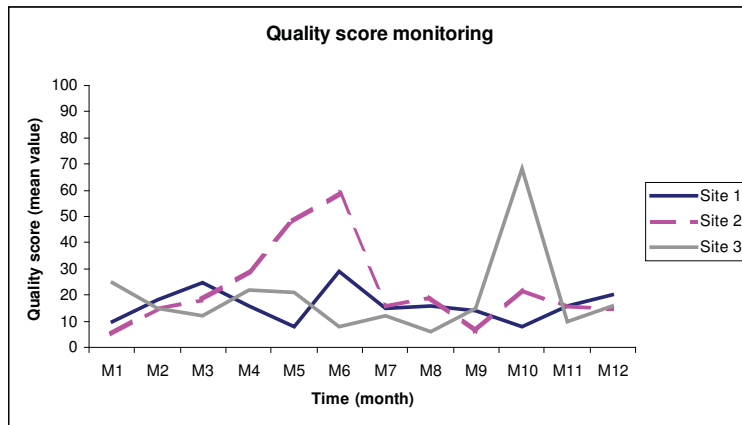
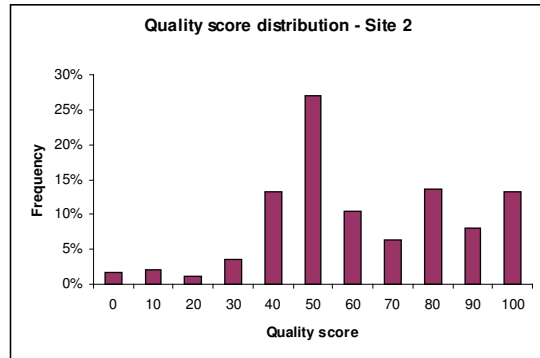


Fig. 4: Graph showing quality monitoring for a long duration study

Fig. 5



Fig. 6



Graphs to compare quality scores between sites

## Summary

The technological evolution of ECG data collection & analysis is an opportunity to develop new tools for better ECG quality management.

Even though the ECG Warehouse system was not designed for the purpose, it contains perfect material for calculating metrics. The facts and figures available allow a direct evaluation of the performance of the clinical sites and of the ECG Core Lab.

The next step could be to achieve a global standardisation of the metric calculation criteria.

Let us encourage initiatives such as Metric Champion Consortium (MCC), already taken into account in Clinical Trials performance evaluation.

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## **Finland Introduces New Hospital Agreement Template**

Pharma Industry Finland (PIF) has, in co-operation with the Association of Finnish Local and Regional Authorities, prepared a new template for agreements for clinical trials. This can be used for making the contracting process smoother with hospital districts and other trial sites in Finland.

The template is most suitable for phase III and IV trials conducted in public healthcare settings. It takes into account relevant local guidance and legislation, covering all the minimum aspects that should be covered by trial agreements concluded in Finland. The template is available in Finnish and in English.

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