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AI-enabled Risk Based Monitoring – Cardiac Safety

ECG Analysis in Clinical Trials

Electrocardiograms (ECGs) play a crucial role in evaluating the cardiac safety of new drugs throughout clinical development. High-quality ECG data are essential for accurately detecting potential cardiac risks, such as QT interval prolongation, arrhythmias, or other adverse effects that could lead to patient safety issues, regulatory concerns or trial discontinuation.

During Phase I studies, ECGs are frequently used to assess the cardiac safety of a new drug, especially for detecting the risks mentioned above. The International Conference on Harmonization of Technical Requirements for Registration of pharmaceuticals for Human Use (ICH) requires all new drugs with systemic bioavailability to be subjected to a clinical evaluation of the QT/QTc interval prolongation and proarrhythmic potential per the E14 guidance.[1]

As a development program progresses to Phase II and III, where larger patient populations are involved, maintaining ECG quality becomes even more critical to confirming a drug's potential long-term cardiac effects and meeting regulatory requirements. Poor ECG quality can lead to an inability to perform an ECG analysis, the misinterpretation of results, and potentially even the failure of promising drugs due to false positive safety concerns from avoidable data inconsistencies.

Risk-Based Monitoring

Risk Based Monitoring (RBM) is an important tool to optimize efficiency and data quality in clinical trials. According to FDA's final **'Guidance for the industry'** document on Risk-Based monitoring, drug sponsors are "required to provide oversight, including ensuring proper monitoring of the investigation." The FDA Guidance notes that "[s]uch oversight helps to ensure…the integrity of the data submitted to the FDA" and recommends that "sponsors should implement a system to manage…both risks to participants (e.g., a safety problem) and to data integrity (e.g., incomplete and/or inaccurate data)" and that "[t]his system should include a risk-based approach to monitoring tailored to the potential risks for the specific clinical investigation." Finally, the Guidance states that "[e]ffective implementation of risk-based monitoring…should help maximize the quality of a clinical investigation."[2]

AI-enabled Risk Based Monitoring

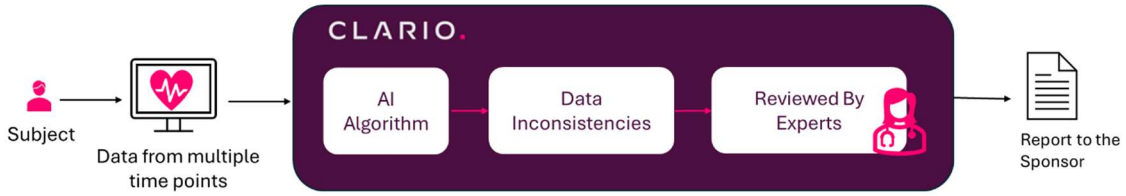
Patient Identification and Fingerprinting

Every individual ECG exhibits distinct characteristics, creating a unique ECG pattern. ECG analysis, enhanced by Artificial Intelligence (AI), revolutionizes the detection of ECG data inconsistencies in clinical trials by analyzing the individuals' unique ECG pattern. With the help of AI algorithms, it is possible to analyze and compare these patterns, detecting data inconsistencies and flagging potential areas that require intervention.

ECG data discrepancies identified can then be reviewed and validated by clinical experts culminating in detection of areas that can be improved by targeted retraining programs or comprehensive site reviews. This approach provides a smart and adaptive methodology to uphold data integrity throughout the clinical trial process.

By comparing ECG records from different subjects from the same site using AI, it is possible to signal potential misidentification associated with a specific ECG record, which reduces errors, identifies duplications and enhances data integrity and patient safety.

The use of AI algorithms can also facilitate the detection of significant changes in an individual's ECG profile over time and result in a timely notification to clinical experts for facilitate data review and analysis.



AI algorithms can be used to enhance ECG data integrity, accuracy, and quality control measures across the study. Combined with a manual review by clinical experts, the result is more reliable cardiac safety data, improved decision-making, and enhanced patient safety.

Benefits:

- Detect mislabeled ECGs and patient duplication
- Detect longitudinal changes in patient's ECGs
- Improve data accuracy by ensuring integrity of patient records.
- Enhanced data quality
- Optimized workflow for efficiency

AI-powered ECG Quality Score

Given the critical position an early-phase trial has in determining the probability of success and continued development of a new drug entity, it is essential that the data generated at this phase are complete, usable and reliable. Any steps taken to enhance data quality in early phase development can increase the return on investment if those efforts prevent an asset from failing inappropriately or clearly

support appropriate termination of a program.

Every drug in development will have to undergo testing to evaluate its potential to prolong the QT interval. Early-phase ascending dose studies offer an optimal opportunity to collect ECG data to investigate a potential effect on the QT interval. In these studies, high drug exposures are obtained that potentially cannot be reached in later studies. As new drugs most often fail in Phase I, sponsors may decide not to analyze the phase I ECG data until they have a better understanding of the pharmacokinetics and efficacy of their compound. If the strategy selected is to collect, clean, and store the continuous ECG data for later analysis, it is important to assure the data are of good quality and will be useful to support a future analysis in pursuit of a TQT waiver. In contrast, ECG quality can be assessed during study conduct between dosing cohorts. For example, if after completion of the first dose cohort a quality issue is identified, there is opportunity to implement corrective actions (e.g., site retraining, device replacement) before advancing to higher dose cohorts, when the potential for QT interval prolongation and toxicity is highest.

Clario has developed an AI-powered tool to automatically check the quality of continuous ECG recordings. Using an AI-powered tool can increase the overall quality of ECG data from a study and reduce the risk of challenges in the clinical trial process due to missing or incomplete data.

Benefits:

- Allows earlier assessments of cardiac safety data quality
- Offers valuable insights and reassurance to sponsors by enhancing data quality assurance, reducing risks, and ultimately improving the likelihood of a definitive cardiac data analysis result
- Provides actionable insights to sponsors, enabling proactive remediation and reassurance as to data quality

This AI-powered tool can also be used as a complement to Clario's industry-leading Early Precision QT® (EPQT) solution. EPQT enables earlier and more precise QT assessment with smaller sample sizes and lower cost. This facilitates the assessment of QT/QTc interval prolongation and proarrhythmic potential of investigational products required by health authorities for approval.

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References

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2. Food and Drug Administration. A Risk-Based Approach to Monitoring of Clinical Investigations Questions and Answers. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/risk-based-approach-monitoring-clinical-investigations-questions-and-answers. Accessed April 2, 2025.