



## WHITE PAPER

# Centralized ECG Collection and Analysis in Clinical Investigation: An ROI Analysis

Sponsored by: eResearchTechnology

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## EXECUTIVE SUMMARY

The use of centralized core labs for the collection and analysis of ECGs in "thorough QT/QTc" studies is commonplace in the pharmaceutical industry. Increasingly, clinical operations managers are choosing to continue using centralized core labs for collection of ECGs in subsequent clinical studies, regardless of the outcome of the thorough QT/QTc study. There is also significant use of central labs in studies prior to a thorough QT/QTc study. Although this use is not specifically required by current regulations, the benefits of the rigorous analysis provided by ECG core labs are becoming increasingly clear to clinical research stakeholders.

A recent study conducted by Life Science Insights and sponsored by eResearchTechnology, a leading ECG core lab, has shown promising economic and practical benefits from the centralization of ECGs in Phase II and III clinical studies. These benefits include:

- Costs that are equivalent to or less costly than those of decentralized ECG collection and analysis
- Improved data quality and time savings for ECG analysis in clinical studies
- Increased accuracy of analysis for ECGs, providing confirmatory statistical power for negative "thorough QT/QTc" studies
- Continued, rigorous evaluation for drugs shown to have positive results during "thorough QT/QTc" studies, as required by regulatory agencies
- Convenience and access for clinical sites with limited cardiology resources

The study focused on an interview-based approach to determining the quantitative and qualitative data that demonstrates this value proposition.



## METHODOLOGY

This white paper is based on the results of a recent study conducted by Life Science Insights and sponsored by eResearchTechnology, a leading ECG core lab. The objectives of the study were to examine and develop estimates of the return on investment (ROI) for using centralized core labs in the collection of ECGs primarily in Phase II and III clinical studies. The study consisted of interviews with individuals involved in the clinical research process, in Phase II and III studies, and in pharmaceutical and biotech companies. Targeted clinical trial professionals included those associated with the ECG portion of a clinical trial. Those categories consist of:

- ☒ Clinical operations specialists
- ☒ Clinical research associates (CRAs)
- ☒ Data managers
- ☒ Financial specialists

These four areas of specialty represent the large majority of people working with the ECG portion of the trial. These roles are defined in the Definitions and Acronym Glossary at the end of this document.

In contacting these specialists, we aimed to speak with a variety of research environments to get a distribution of samples. We spoke to 24 people from 15 companies of various sizes — midsize to large — in pharma and biotech. We focused our interviews on people with experience primarily in Phase II and III, and we spoke to people who cited experience in many therapeutic areas.

To interview people in each of these areas, we followed a drafted set of questions tailored for each category, focusing on the specialists' respective efforts associated with the ECG portion of their responsibilities and captured the time associated with each of their activities. We then captured the amount of time they were displaced from their activities when trials incorporated a centralized ECG vendor. That data became the foundation of our research.

To fully understand further details of the efforts associated with the ECG portion of these trials, we followed up the interviews with phone calls and emails to capture the full picture. These follow-ups completed the picture for us and also allowed us to validate our earlier findings. From these follow-up contacts, we were able to capture some key data points, especially regarding queries.

Upon finishing the follow-ups, the complete assessment of the effort dedicated to the ECG portion of clinical trials allowed us to ascertain the displaceable portion of those efforts, which makes up the financial value proposition in switching from local to centralized ECGs.

## IN THIS WHITE PAPER

This white paper presents data from a recent study conducted by Life Science Insights and sponsored by eResearchTechnology, a leading ECG core lab. The study aimed at understanding and evaluating the value proposition for the centralization of ECG core lab services in clinical studies outside the thorough QT/QTc area.

The Situation Overview section of the paper presents a review of the existing regulatory requirements and their application to these types of studies. It also presents an overview of processes for collecting, analyzing, and verifying ECG data in both local and centralized research environments. The Study Findings section of the paper presents qualitative and quantitative data derived from the primary research study.

## SITUATION OVERVIEW

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### Regulatory Requirements

The use of ECGs, and specifically the QT/QTc interval, as a biomarker for cardiac safety of new drugs is the result of several catastrophic drug safety failures. In its May 2005 publication of the E14 guideline, *The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs*, the International Conference on Harmonisation (ICH) set forth requirements for thorough studies of the QT/QTc interval. This document has served as a guide for pharmaceutical companies submitting drugs for approval to the FDA, EMEA, and Japanese Health Ministry since its publication.

The E14 guideline clearly lays out the principles for executing a thorough QT/QTc study and recommends the involvement of an ECG core lab in these evaluations. ECG core labs are widely used in thorough QT studies. However, E14 leaves further ECG collection and analysis requirements quite vague, referring only to "collection of on-therapy ECGs in accordance with the current practices in each therapeutic area to constitute sufficient evaluation during subsequent stages of drug development" (E14, page 6) as guidance for evaluation following negative thorough QT/QTc studies. Although the methods described in the E14 guideline are not required by the rule for evaluation of later ECGs, their merit, combined with concern by industry experts about the quality and nature of on-therapy ECG collection and analysis in some therapeutic areas, has led many pharmaceutical companies to consider cardiac data risk management strategies that include more rigorous analysis of ECGs in subsequent stages of clinical research than specifically required. This white paper addresses the value of using ECG core labs in Phase II and Phase III studies other than thorough QT studies.

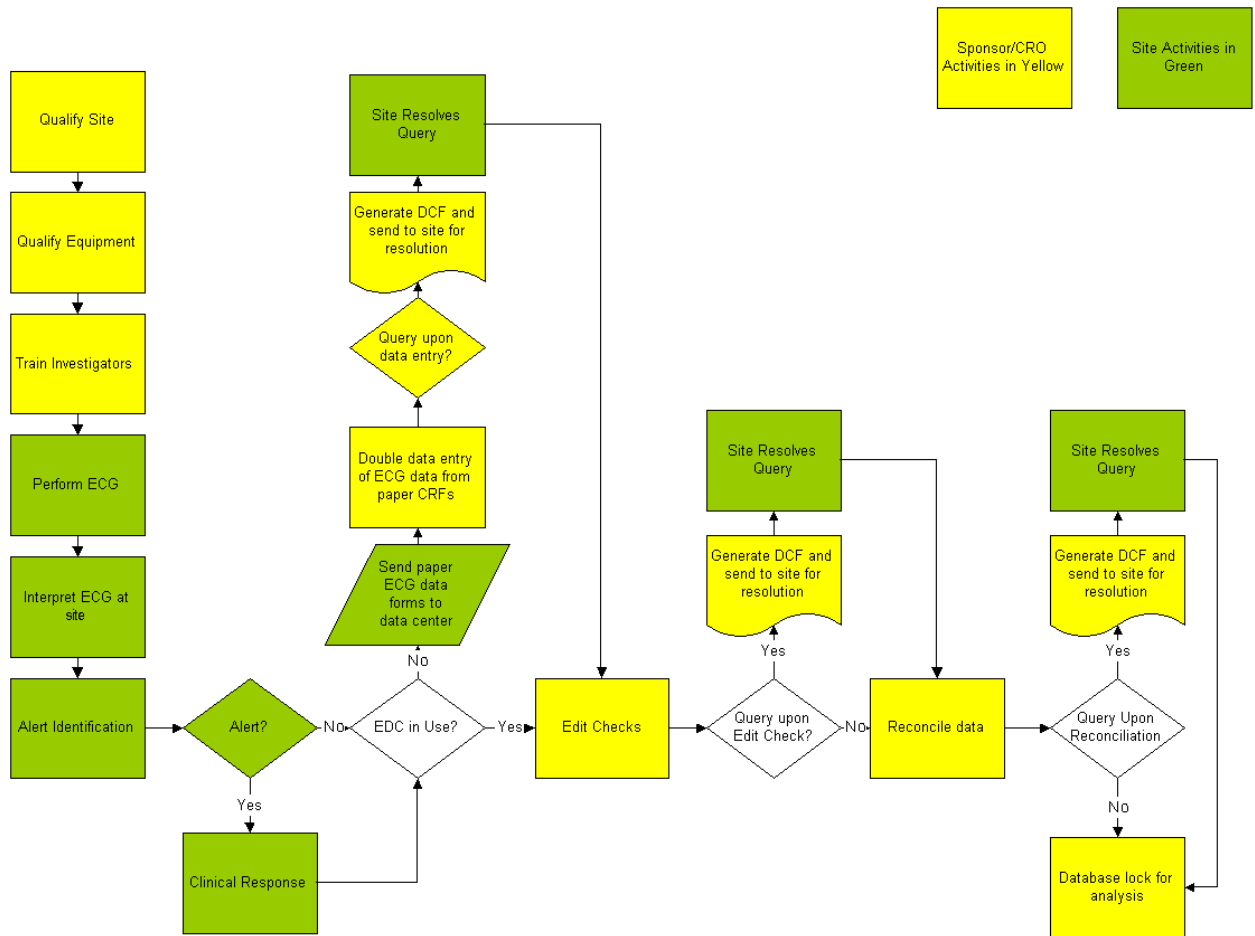
# ECG Collection and Analysis Processes

## Local/Decentralized

The local/decentralized process for ECG collection can represent a tedious process; the entire burden of work for ECG collection lies with the sponsor/contract research organization (CRO) and clinical research site. The process itself represents over a dozen separate steps as shown in Figure 1. The sponsor's responsibilities in the manual process include qualifying sites and equipment, training investigators, generating queries and edit checks and their accompanying manual data correction forms (DCFs), reconciling data, and performing the actual management of the ECG database and database lock. The site's responsibilities include performing the ECG, interpreting the ECG, generating initial medical alerts, documenting the ECG on a CRF in the trial book (if EDC is not used), and responding to several series of later queries generated by the sponsor/CRO.

**FIGURE 1**

Decentralized ECG Process



Source: Life Science Insights, 2005

### ***Centralized***

In the centralized process, an ECG core lab takes the bulk of the work from the sponsors/CROs, reduces the workload for sites, generally simplifies the overall ECG collection and analysis process by utilizing digital ECGs, and ensures effective management of the alert and query processes. A comparison of the central and decentralized processes is provided in Table 1.

In addition to the shift in physical workload that occurs when sponsors move from decentralized ECG processes, several significant data quality improvements also occur:

- ☒ Providing qualified equipment to sites and performing centralized training ensures that all sites have comparable, well-calibrated equipment, which reduces measurement errors that may occur when this process is decentralized and sites are using nonstandard equipment.
- ☒ The automatic alert process reduces the possibility of mistakes in clinical analysis — for noncardiac drugs, investigators may not have the expertise needed to interpret ECGs. When a core lab is used, every ECG is seen by a qualified cardiologist, ensuring that clinical action is taken when cardiac changes are observed on the ECG.
- ☒ Removing manual data entry from a CRF by using digital ECGs minimizes the number of queries and the time elapsed between the ECG measurement and those queries that do occur. Thus, clinical responses to fewer, more timely queries can be generated more quickly and easily.
- ☒ CRAs involved in local ECG studies indicated that they did not always feel qualified to monitor documentation of ECG data on CRFs — using a core lab ensures that all documentation is done by individuals familiar with ECG data.
- ☒ Automated query processes significantly accelerate the time to sign-off and database lock.

**TABLE 1**

## Process Comparison: Decentralized Versus Centralized

Task	Actor — Decentralized	Actor — Centralized
Qualify sites and equipment	Sponsor/CRO	ECG Core Lab
Train investigators	Sponsor/CRO	ECG Core Lab
Perform ECG	Site	Site
Analyze ECG and generate medical alerts	Site	ECG Core Lab
Clinical response to alerts	Site	Site
Document ECG	Site	ECG Core Lab
Generate queries	Sponsor/CRO	ECG Core Lab
Respond to queries	Site	Site
Reconcile data — second round of queries	Sponsor/CRO	ECG Core Lab
Database management (ECG portion)	Sponsor/CRO	ECG Core Lab
Sign-off on final data (ECG portion)	Site	ECG Core Lab
Database lock (ECG portion)	Sponsor/CRO	ECG Core Lab

Source: Life Science Insights, 2005

## STUDY FINDINGS

### Qualitative Aspects of Return on Investment from Centralized ECGs

Qualitative data collected during primary research consisted of the collective input of the clinical operations specialists, CRAs, and data managers with whom we spoke.

#### *Clinical Operations Specialists*

Clinical operations specialists interviewed as part of the study cited perceived benefits from the use of ECG core labs that included:

- Decreased site and sponsor workload
- Reduction in variation between equipment used at sites
- Consistency in measurement and analysis — getting consistent reads from the same people at a centralized analysis site



Data managers also mentioned some challenges that arose as the result of core lab involvement in the ECG analysis. Most of the challenges involved communication between sponsor/CRO data managers and the core lab and included:

- ☒ Careful selection of qualified core labs in order to meet expectations of sponsor and site personnel
- ☒ Thorough understanding of requirements for both core lab and data management
- ☒ Need to train ECG core lab on company standard operating procedures (SOPs) to ensure compliance with data management and query handling
- ☒ Issues with data migration into the sponsor's/CRO's platform following the completion of the trial

On the whole, most of the data managers we spoke with emphasized that although centralization created challenges, the benefits to both cost and data quality likely outweighed the potential problems.

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## **Quantitative Analysis of Return on Investment from Centralized ECGs**

In collecting quantitative data during the study, we developed metrics that focused on understanding the displaceable costs that are available when trials switch from decentralized to centralized ECGs. Quantitative data collection focused on the following metrics:

- ☒ **Clinical operations specialists.** Clinical operations specialists were asked about the amount of time spent on managing the ECG component of the trial, mainly alerts and queries, in a decentralized ECG environment. Specific metrics included effort/staff requirements, time, and cost.
- ☒ **CRAs.** CRAs were asked about the amount of time spent on monitoring the ECG component of the trial and managing alerts and queries in a decentralized ECG environment.
- ☒ **Data management.** Data management interviews focused on capturing the amount of time spent on managing the study-end data for the ECG component of the trial in a decentralized ECG environment. Metrics included query time and reductions in time to database lock.
- ☒ **Financial specialists.** Financial specialists were asked about contracting and budgeting for trials with centralized ECGs. Specific metrics included investigator payments and equipment reimbursement.

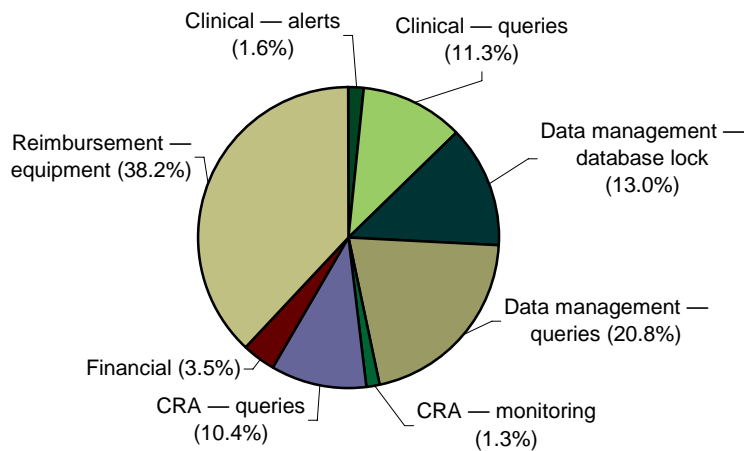
In the individual categories of expenses studied, equipment reimbursement represented the single largest displaceable cost. This category included displacement of payments to local sites for the use of their existing ECG equipment and associated supplies (e.g., leads, paper) that was replaced by standardized, professionally calibrated equipment and supplies provided by the ECG core lab, generally at lower cost. The payments for equipment averaged about \$32.00 per ECG and were displaceable when studies were centralized.

Data management savings represented the next largest category. They consisted of savings from the reduction in the number of queries as a result of automation and a reduction in the time to database lock as a result of the automation of queries and data reconciliation.

The data management category was followed by clinical savings, which resulted from the removal of local analysis of the ECGs as well as the reduction in the number of queries and time elapsed between completion of the ECG and query generation. CRA monitoring costs also benefited from these efficiencies. A summary of all the displaced costs is presented in Figure 2 and Table 2.

**FIGURE 2**

Savings from ECG Centralization



**Total savings = \$84/ECG**

n = 24

Note: Savings are expressed per ECG, based on the average of respondents.

Source: Life Science Insights, 2005

**TABLE 2**

## Summary Data: Savings from ECG Centralization

Savings Area	Per ECG (\$)
Clinical — alerts	1.36
Clinical — queries	9.47
CRA — monitoring	1.09
CRA — queries	8.70
Data management — database lock	10.87
Data management — queries	17.39
Financial	2.94
Reimbursement — equipment	32.00
<b>Total</b>	<b>83.81</b>

n = 24

Source: Life Science Insights, 2005

**FUTURE OUTLOOK****Trends**

In recent months, high-profile events such as the withdrawal of Vioxx have pushed the FDA and its oversight of the drug approval process into the spotlight. One element of this increase in oversight is an emphasis on drug safety in clinical trials, particularly cardiac safety. In the measurement of ECGs during trials, the QT biomarker is a critical component, yet the nature of its measurement makes 100% accuracy difficult. ECG core lab services have the potential to increase the accuracy of QT/QTc interval measurement and ECG interpretation at all stages of trials, and the overall sentiment is "better safe than sorry" in the case of accuracy and centralization. This trend is reinforced by the data in this study, which presents financial justification for increased levels of centralization.

An additional trend lies in a general increase in the overall use of technology in trials. In the past year, Life Science Insights' studies reflect a growth in the use of EDC in clinical trials by about 13–16%. Increased use of digital ECGs and core lab analysis technology is an extension of this technology trend.

Additionally, the potential that there will be further regulatory guidance on the use of more rigorous analysis of ECGs in all trials exists. Many companies believe that moving toward centralization protects their development projects in the event that the requirements for ECG analysis are increased.

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## **Technology**

ECG technology is ever improving, and the trend is to utilize new technology as it becomes available. This trend is seen in the increased use of digital ECG systems, ECG analysis software systems, and continuous Holter monitors for ECG monitoring. ECG core labs are also able to provide ECG collection equipment that is more closely optimized for clinical research. These systems will continue to add to the accuracy and ease with which more in-depth and more frequent monitoring of ECGs can occur during clinical trials.

ECG core labs have the potential to improve access to the most current technology options for ECGs; however, buyers should beware of low-cost core lab services that may use out-of-date equipment and applications.

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## **Challenges**

ECG core labs providing services to clinical trial sponsors face the challenge of balancing the rising cost of clinical development with a need to provide accuracy and high-quality services. ECG core lab processes are increasingly standardized, and core labs are challenged to differentiate themselves on dimensions other than price.

Although there is a clearly demonstrated ROI from ECG core lab services, the services provided and costs for providing them will in some cases exceed the measurable ROI, whether literally or conceptually in a particular instance. In these cases, the argument will always be won on the basis of the qualitative benefits of ECG core labs. Proving that the major qualitative improvements from centralization — improvements to data quality and lessening of effort on the part of sites and sponsors — are of sufficient value to justify the expense will be a critical challenge for core labs. This challenge is particularly evident in the case of studies such as those examined in this white paper — where the regulatory requirement does not explicitly exist for the rigorous level of analysis that ECG core labs provide.

## **CONCLUSION**

The results of this study presented a clear ROI for the centralization of ECGs in Phase II and III clinical trials that are outside the thorough QT/QTc area: An average savings of \$84.00 per ECG can be attributed to centralization when collection and analysis are outsourced to an ECG core lab.

The per-ECG cost for core labs was generally below the \$84.00 savings estimate, but fell within a range of \$70.00–120.00. Pricing for ECG core lab services depended on the specific clinical research situation and requirements and the technology used. The cost quoted by the core lab is affected by the duration of the study, the number of ECGs per site per month during the study, the quality of the equipment leased from the core lab, and the size of the relationship between the core lab and the sponsor. The core labs that were consulted included the study sponsor, eResearchTechnology, as well as three other core lab facilities.

The qualitative benefits of using ECG core labs were also examined in this white paper.

## DEFINITIONS AND ACRONYM GLOSSARY

**Clinical operations specialists.** Clinical operations specialists handle the operational management of the study and monitor and manage any ECG queries and alerts from the trial.

**Clinical research associates.** Clinical research associates (CRAs) monitor the study at the level of protocol compliance, ensuring the ECGs are performed and validated by the principal investigator, and generate queries if and when necessary.

**Data managers.** Data managers are involved in the ongoing review of ECG data. As patients complete their ECGs, data flows to the sponsor, where the data management department reviews the ECG data for acceptability of format, protocol compliance regarding the timing of ECG, and such items. Data managers also work vigorously to lock the database with "clean" data after the final patient has completed the trial.

**E14 guideline.** The ICH's E14 guideline, *The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs*, was published in May 2005. It provides internationally accepted guidance as to the use of thorough QT/QTc studies in clinical research and the specific conduct of these studies.

**ECG.** An electrocardiogram exam, or ECG, is an examination in which electrical leads placed on the torso of the human body measure the electrical impulses of the heart for diagnostic purposes.

**EMA.** The European Medicines Agency (EMA) is a decentralized body that governs drug approvals for medicinal products in the European Union.

**FDA.** The Food and Drug Administration (FDA) is the government agency that oversees the regulation of prescription drugs, biologicals, and devices marketed in the United States.

**Financial specialists.** Financial specialists are involved in negotiating the payment per ECG (inclusive of equipment costs and labor) to the sites.

**ICH.** The International Conference on Harmonisation (ICH) is the international organization governed by representatives from pharma in the three main drug-consuming regions — the United States, Japan, and European Union — that sets international requirements for the common technical document, preclinical, and clinical trial processes.

**QT interval.** The QT interval represents the "duration of ventricular depolarization and subsequent repolarization" (E14 guideline) and refers to the measured time of a specific portion of a human heartbeat. Lengthening of the QT interval, in the context of the action of a specific drug, represents a biomarker for the drug's increased potential to cause heart arrhythmias, particularly *torsade de pointes*.

**QTc interval.** The QTc interval is defined in the E14 guideline as the QT interval corrected to reflect a standardized heart rate of 60 bpm.

**Sponsors/trial sponsors.** The term *trial sponsors* refers to the pharmaceutical, biotech, and medical device companies that are the sources of financing for clinical trials, whether they conduct the trials by contracting with individual investigators or by outsourcing these responsibilities to a CRO.

**Thorough QT/QTc study.** A thorough QT study is a single clinical trial, usually conducted on healthy volunteers during Phase II of a drug's development, that specifically and precisely evaluates the drug's effect on the QT/QTc interval. The central analysis requirements of the thorough QT/QTc study set forth in the E14 guideline generally require the use of an ECG core lab for this particular study.

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