Navigating ECG Cardiac Safety Requirements

To prevent the risk of induced arrhythmias in cardiac drug development, it is important for developers and biotech companies to adhere to ECG safety requirements in early stage research

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Cardiac safety study requirements apply to almost all drugs in every therapeutic area, not just cardiology. Their aim is to prevent the approval of drugs liable to increase the risk of sudden cardiac death from serious arrhythmias induced by novel agents with unrecognised electrophysiological effects.

These studies matter at every stage of drug development. Even at proof of concept, a biotechnology startup can increase investor interest by demonstrating electrocardiogram (ECG) safety up front. However, since the 1990s, guidance has evolved and uncertainty abounds regarding the correct testing approach. Here, we discuss cardiac safety best practices and how developers can avoid delays from lengthy QT studies as filing time approaches, when overheads are highest.

How Cardiotoxic Drugs Changed the Regulatory Landscape

In the 1990s, adverse event data flagged several drugs as potential cardiac bad actors. These were not obscure medications, but rather drugs with everyday applications. Terfenadine and astemizole were new, non-sedating antihistamines, grepafloxacin was a broad-spectrum antibiotic, and cisapride was a remedy for gastroesophageal reflux. These drugs in overdose, in patients with altered drug kinetics such as the elderly, or in certain drug combinations, caused QT interval prolongation and potentially fatal cardiac arrhythmias. Between 1998 and 2000, manufacturers withdrew these drugs from the market (see **Figure 1**).

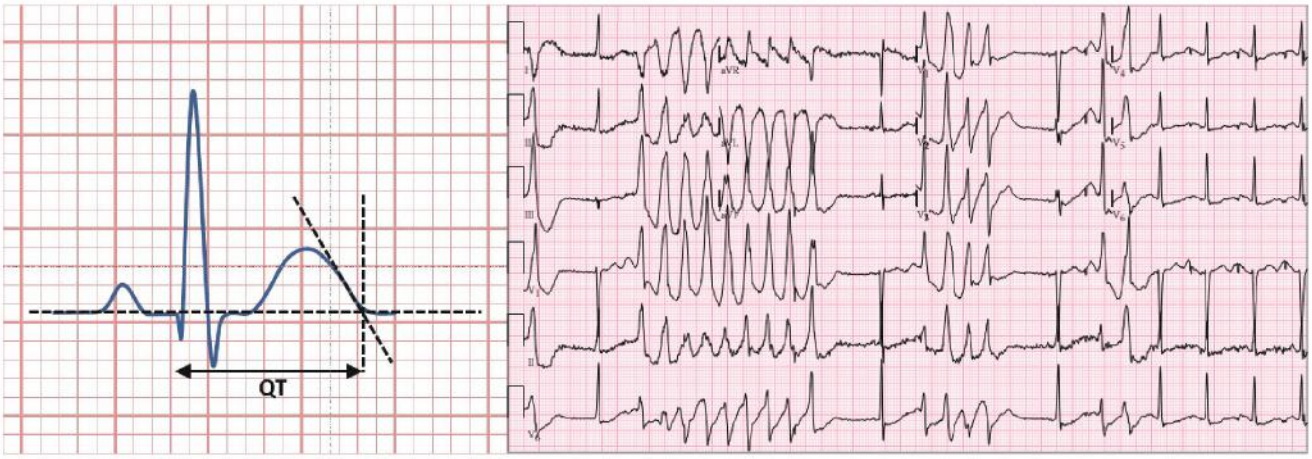

Figure 1: The QT interval marks the duration of electrical depolarisation and repolarisation within the heart muscle as it contracts and recovers (left). QT prolongation is associated with impending severe cardiac arrhythmias such as 'torsades de pointes' (right). *Source: Courtesy of Jason E Roediger, CCT, CRAT*

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Factor	EM is better option	TQT is better option
Time/cost critical		
Clinical dose hard to predict		
Tmax highly variable		
Multiple days of dosing required		
Crossover not possible		
Only relatively low exposure attainable		
Delayed ECG effect (hysteresis)		
Very long half-life		
Multiple or unknown active moieties (e.g., herbal)		

Table 1: Factors important in selection of CEM vs TQT

From 1997 onwards, the FDA, the ICH, and Health Canada issued guidance recommending preclinical and clinical evaluations of drug-related prolongation of repolarisation, but did not specify how to perform such testing. It wasn't until 2005 that more concrete recommendations emerged in the joint FDA/ICH E14 publication.

To evaluate a new drug's potential to cause severe arrhythmias, this E14 guidance called for thorough QT (TQT) studies evaluating ECGs for QT prolongation in response to increasing plasma concentrations of active pharmaceutical ingredients. QTc, the QT corrected for heart rate, has long been used in drug development as a biomarker for cardiac safety. Since ECG analysis was mandated, the public has benefitted: QT-prolonging drugs have been identified prior to marketing, and clearly labelled as such.

New, Streamlined Method for Demonstrating Cardiac Safety

Since 2005, the guidance for industry has evolved, offering alternative ways to fulfil cardiac safety requirements – an important advancement as standard TQT studies are costly. Chapter five of the 2017 E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs – Questions and Answers (R3) document outlines the use of concentration response modelling (also known as concentration effect modelling [CEM] or C-QT) for cardiac safety assessment in drug development (1). When appropriate, developers can obtain TQT waivers by performing this type of evaluation.

CEM is an analysis usually performed at the start of clinical development by adding robust ECG methods and frequent ECG recordings during the escalating dose, first-in-human (FIH) pharmacokinetic (PK) study. This efficient method establishes the risk of a drug prolonging the QT interval at a wide range of plasma concentrations. Using modelling techniques, concentration data collected during PK studies are compared with time-matched ECG data to determine the exposure-response relationship.

Frontloading this investigation onto FIH studies carries advantages over later-phase TQT studies:

- The drug's electrophysiologic safety is determined before many study patients are exposed
- The time, effort, and cost of Phases I and II are saved if prohibitive ECG effects manifest
- Sponsors may be more willing to bring promising drugs with nonclinical ECG signals (questions of ECG effects raised during preclinical

investigations) to the clinic if they know that the ECG question will be resolved early
- Nonclinical observations that prove not to be true clinical safety issues are less liable to trigger rejection of potentially safe and effective treatments
- Financial and time investments for CEM are much smaller than for TQT
- Knowing the drug's electrophysiologic risk profile can raise asset value for investors looking to purchase the product after proof of concept

Replacing the Standard TQT Pathway With CEM Methodology

Assuming the drug is not one for which QT testing makes no sense (e.g., antiarrhythmic drugs that intentionally prolong QT), its cardiac safety must be evaluated.

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Table 1 (page 57) summarises the weight of various factors in favour of CEM or TQT.

To summarise, a standard TQT study is preferred when:

- The drug's effect on ECG occurs an hour or more after the maximal plasma concentration (Cmax) is achieved (hysteresis)
- A long half-life means that ECG measurements must be performed over days to weeks, increasing the possibility of ECG changes unrelated to a drug effect
- The active chemical entity is unknown as plasma levels can't be measured or related to ECG events
- Multiple doses are required to achieve adequate supratherapeutic levels or such levels are unattainable
- The sample size is too small to cover the range of plasma concentrations needed for verification

CEM is useful when:

- In a drug with unpredictable or random Tmax, the time-point oriented analysis might miss a substantial ECG effect because it would be diluted across time, whereas the CEM method would capture the relationship of drug concentration to effect
- Cost is key; for a single dose with four dose levels, CEM methods cost about a half to two-thirds as much as standard TQT because there are usually fewer participants with shorter confinements
- Speed is paramount
- ECG is piggybacked onto PK studies and the Phase II TQT study is eliminated
- Each parallel arm is completed independently with a single cohort
- Most TQT studies take longer because of multiple cohorts with washout periods
- The FIH single and multiple ascending dose studies have already been done; though repeating PK studies seems wasteful, it may still be more economical than TQT studies
- Previously gained safety and tolerance data can help inform a streamlined CEM design
- Finding a knowledgeable partner is key in evaluating all the pros and cons and coming up with the best plan of action for the drug development project and situation at hand

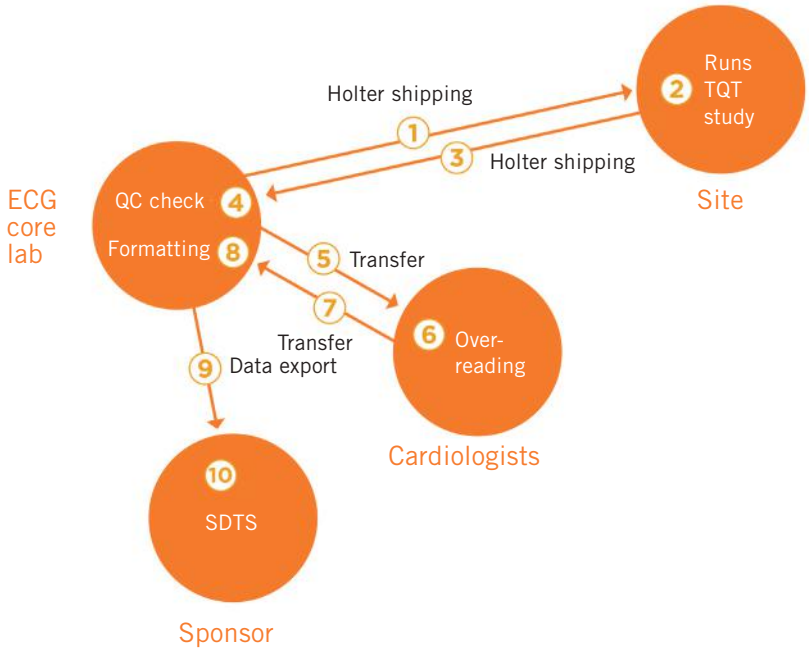

Figure 2: Workflow for the standard model for obtaining and processing ECG data from Holter monitoring in a TQT cardiac safety study – time from last subject out to data receipt by sponsor is 2-3 months

The following are cases that illustrate reasons for choosing one pathway over the other:

Limited Funding
When the sponsor has tight resources initially, it might make sense to withhold ECG studies until Phase III, delaying the expense until a partner comes on board and provides additional funding.

A Preclinical Signal Has Occurred
If something has happened, such as QT prolongation in a safety pharmacology study in dogs, but the drug has great potential, it may be necessary to show the ECG is clean or to clearly define the extent of its ECG effects in humans early on (e.g., by doing a CEM analysis during the FIH study).

Dosage in FIH Turns out to Be Barely Therapeutic
Since the effective dose of a new drug is uncertain, the original FIH protocol's dosages may be lower than the actual effective dosage determined later, or they may not be supratherapeutic enough (2x-5x) to satisfy regulatory requirements for cardiac safety studies. Luckily, there is a relatively simple remedy: if CEM was done, the studies won't have to be repeated completely. A few more higher-dose cohorts will need to be added to satisfy FDA requirements.

eSource-Enabled ECG

Regardless of pathway, robust cardiac safety studies are impossible without dependable ECG testing that produces comparable results. Reliance on an assortment of equipment types and operators with indifferent readers, all operating independently, is unwise. For convincing results, a centralised ECG function, with comparable equipment, supported by well-trained, consistent readers is a must; it is specifically required by the E14 mandate.

A clinical research partner that specialises in integrating clinical trials with cardiac care can guide drug developers in the most accurate, timely, and cost-effective cardiac risk assessment pathway for fast-paced Phase I trials and throughout clinical development.

The workflow presented in **Figure 2** shows a comparison between the traditional model for obtaining cardiac safety data through Holter studies and the ECG eSource model that utilises direct, electronic ECG capture, highlighting the eSource method's efficiencies.

1. ECG core lab ships Holter monitors to site (1-2 weeks)
2. Site runs TQT study (1-3 months)
3. After last ECG, site assembles Holter flash cards and ships back to core lab (2 weeks)
4. ECG core lab quality control check (1 week)
5. Over-reading by cardiologists (1-2 weeks)
6. Over-read complete (1 day)
7. ECG core lab formats according to data transfer specifications (1-2 weeks)
8. ECG core lab exports data to sponsor
9. Sponsor may have to format according to standard deviation of time series (2 weeks)
10. Statistical analysis of ECG data (2-3 weeks)
11. Topline results

Figure 3 shows the integration of Phase I, biometrics, and ECG core lab services for a TQT cardiac safety study.

1. Data livestreamed at the ECG core lab and stored in uniform database eliminates shipping and formatting tasks

a. Onsite telemetry technicians monitor data live, which enables prompt troubleshooting to ensure the quality of ECG waveform, preventing data loss

2. Cardiologists start reading immediately, entering their input within 24-48 hours
3. About two days after the start of data collection, sponsors can access live view. Preliminary results:

a. Allow for adaptive design

b. Allow sponsors to report critical cardiac safety trends to stakeholders

4. Statistical analysis begins
5. Last subject, last visit

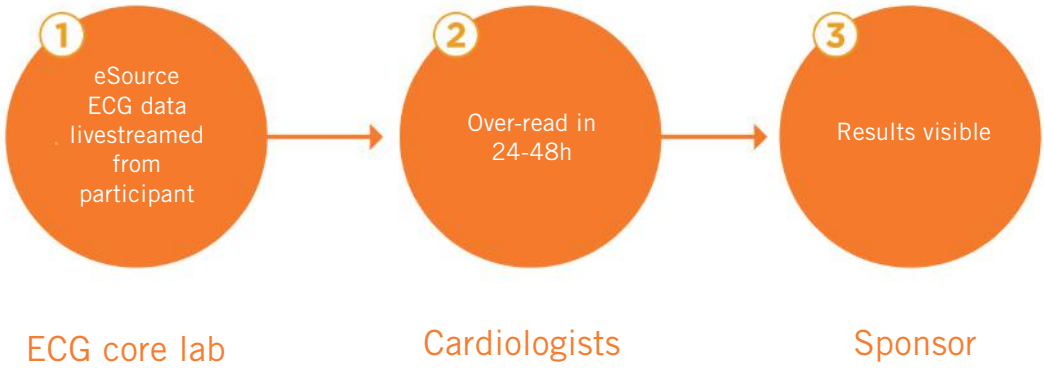

Figure 3: Integration of Phase I, biometrics, and ECG core lab services for TQT cardiac safety study: Time from last subject out to topline results is 2 weeks

6. Topline results
7. SDTM-compatible results enable statistical analysis to begin at the time of last ECG collection – not two months thereafter. Final clinical study report is produced 1.5 months after last patient out, around two months earlier than standard Holter protocol

A well-seasoned, responsive, and agile team implementing an established, fully integrated eSource ECG system is key for producing quality cardiac safety data quickly. Paperless electronic data capture reduces errors, supports faster results, and decreases expenditures on data cleaning and extra clinical monitoring for even the most complex studies. The result is faster decision-making and less spending on overhead while results are pending.

Conclusion

Drug developers now have options for how to meet FDA cardiac safety mandates. A standard TQT is not appropriate in all circumstances, nor is CEM always the fastest pathway. Many factors affect which choice is appropriate and why, from the intrinsic characteristics of the drug candidate to company finances and time constraints. A partner that specialises in this area can help developers make the most advantageous decisions.

In general, for best results, developers should:

1. Start planning ECG assessments early, well before FIH
2. Work with a Phase I facility that has a core lab on-site to save time and resources
3. Realise that a core lab with eSource ECG is highly efficient for both early and late cardiac safety studies
4. Consider that investors may place a higher early value on a product if ECG risk is already known

Whether it's TQT or CEM, technology integration and eSource can produce critical preliminary and final results much faster than the traditional model.

References

1. *Visit: www.fda.gov/media/71379/download*

Cardiac safety study step	eSource ECG	Industry expectation
System build to first subject screened	4 weeks (28 days)	12 weeks (84 days)
Flash reporting essential data for go/no-go decisions	7 days	3 weeks
Last subject, last visit to final clinical study report	45 days	90 days

Table 2: Time savings of integrated Phase I, biometrics, and ECG core lab services – 55 days (about 2 months)

Jay W Mason, MD, is a world-renowned cardiac drug safety expert with over 45 years of experience in cardiac care/research, and he has authored hundreds of articles on cardiac repolarisation and the overall diagnosis of 'torsades de pointes'. A former medical director at Covance Cardiac Safety Services, Jay is Professor of Medicine (Cardiology) at the University of Utah, US, Chief Medical Officer at **Spaulding Clinical Research**, and an independent consultant in cardiac safety.

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