Cardiac adverse drug reactions are typically serious and can be fatal. Reports of sudden cardiac deaths resulting from several licensed drugs, including macrolide antibiotics, cisapride, terodiline, bepridil, and terfenadine, led to marketing withdrawals in the UK and the US in the 1980s and 1990s. These fatalities prompted concerted regulatory attention that led to the release in 2005 of ICH Guidelines S7B, addressing nonclinical assessment of an investigational drug’s proarrhythmic liability, and E14, addressing clinical assessment of this phenomenon as operationalised by the cardiac safety biomarker QT interval prolongation as seen on the surface electrocardiogram (ECG). The E14 Guideline requires the vast majority of new drugs with systemic bioavailability to undergo a rigorous Thorough QT/QTc (TQT) study specifically designed for such assessment. Typically, these TQT studies are done in parallel with Phase IIb studies after proof-of-concept has been established and the pharmacokinetic profile, maximum tolerated dose (MTD), and proposed therapeutic dose are determined in Phase I/II studies. However, it is recommended that sponsors start collecting high-quality ECG, and hence QT interval data, in their early-phase trials since these provide the best opportunity to assess effects at the widest range of doses usually evaluated in early-phase safety/tolerability studies.

Reliable observation of an unacceptable degree of QT interval prolongation in these early-phase trials can enable a stopping decision for the clinical development programme to be made at the earliest possible timepoint, thereby avoiding subsequent costly time and resource investments in the molecule. Alternatively, and also of considerable benefit, if a decision is made to continue development these initial data permit the subsequent TQT study to be designed in the most resource-efficient manner while preserving full scientific integrity. A good initial understanding of the degree (if any) of drug-induced QT/QTc prolongation, and also the variability in such prolongation seen among subjects, enables the TQT study to be designed with the minimum necessary number of subjects, leading to a less expensive and shorter study and hence a shorter overall clinical development programme.

**Brief Overview of the ICH E14 Thorough QT/QTc Study**

This overview is deliberately short and the material conceptually simplified to emphasise the points of interest in this paper. More detailed discussions can readily be found in other sources.

The parameter QTc represents the measured QT interval (the raw data) ‘corrected’ for heart rate. The QT interval is inversely related to heart rate, but imperfectly so. The QT interval adapts to changes in heart rate over several minutes, a phenomenon called hysteresis. Confounding influences on drug-induced QT interval changes can therefore occur, especially if the drug has a notable effect on heart rate. Various correction formulae have been proposed to ‘correct’ for heart rate, including the commonly used Fridericia (QTcF) and Bazett (QTcB) correction factors, and more recently QTcI, a subject-specific correction methodology in which previously obtained data from each subject are used on a subject-by-subject basis to create the correction factor applied for that subject.

The ‘traditional’ TQT study employs healthy adults and four treatment arms:
- A positive control that is known to increase the QT/QTc interval and hence to demonstrate assay sensitivity. This is typically the antibiotic moxifloxacin.
- The proposed therapeutic dose of the drug.
- A supratherapeutic dose of the drug that is several multiples of the proposed therapeutic dose. This strategy is intended to mimic what may happen in the ‘worst case scenario’ should the drug be approved and taken by patients whose circumstances may lead to greater than intended drug concentrations.
- A placebo.

ICH E14 does not provide unequivocal formulaic instructions on the conduct of the TQT study. Not every TQT study should (or can) be conducted in precisely the same manner. Since its release in 2005, assimilation and interpretation of existing knowledge and the acquisition of new information and related interpretations has proceeded at a quick pace, making the inherent flexibility within the original guidance document meaningful. As it states, “The investigational approach used for a particular drug should be individualised, depending on the pharmacodynamic, pharmacokinetic, and safety characteristics of the product, as well as its proposed clinical use.” This allows sponsors flexibility in the precise design of the study, and increasingly divergent approaches can be seen in the literature. Nonetheless, the basic point of this paper, i.e., that collecting rigorous ECG and hence QT/QTc data in early-phase studies is advantageous, can be made by focusing simply on the drug’s treatment effect and the confidence limits placed around it.

**Placement of Confidence Intervals around the Treatment Effect Point Estimate**

The purpose of the TQT study is to determine whether a drug has a mean effect on QT/QTc interval prolongation that is around the threshold of regulatory concern. The placement of confidence intervals (CIs) around the drug’s treatment effect, which is now known as the treatment effect point estimate, permits this determination.

There are two CIs that can be used in this context: a two-sided 90% CI, and a one-sided 95% CI. Creation of the two-sided 90% CI involves the placement of a lower limit and an upper limit around the treatment effect point estimate. Creation of the one-sided 95% CI involves only the placement of the upper bound of the CI above the treatment effect point estimate, a strategy that is acceptable since primary attention focuses on this upper bound. While consideration of the mathematics of their calculation is not necessary here, the key point to note is that the upper bound of a one-sided 95% CI (as discussed in ICH E14) is equivalent to the upper limit of a two-sided 90% CI.

Consider a TQT study in which the mean drug effect was...
a prolongation in the QT/QTc interval of 7.00 milliseconds (msec), and the mean placebo effect was a prolongation of 1.00 msec (a non-zero placebo effect is common in clinical trials in general). The drug’s treatment effect is calculated as 7.00 msec minus 1.00 msec, i.e., 6.00 msec. To facilitate inference of the degree to which the drug might prolong the QT interval in the general population of patients who would receive it if approved, we now place a two-sided 95% CI around this treatment effect point estimate, or equivalently, place the upper bound of a one-sided 95% CI above it.

A two-sided CI consists of a lower limit that lies below the point estimate, and an upper limit that lies above it. These limits are calculated by subtracting and adding a value, X, from and to the treatment effect point estimate. Imagine that X is equal to 3 msec. The confidence interval is therefore 6±3, which is commonly expressed as follows: 6(3,9). From this result the following statement can be made:

• With 90% confidence, the data obtained from this single TQT study are compatible with a treatment effect (QT prolongation) in the general population as small as 3.00 msec and as large as 9.00 msec, and our best estimate is 6.00 msec.

When using the equivalent one-sided 95% CI, only the upper bound is presented, which in this example is also 9.00 msec. From this result the following statement can be made:

• With 95% confidence, the data obtained from this single TQT study are compatible with a treatment effect (QT prolongation) in the general population as large as 9.00 msec, and our best estimate is 6.00 msec.

The Threshold of Regulatory Concern
The TQT study is designed to look for drug-induced increases of “around 5 msec”10. Operationally, this degree of prolongation is defined by placing a one-sided 95% CI around the treatment effect point estimate obtained from this single study. The “threshold of regulatory concern” stated in ICH E1411 is an upper bound of 10 msec. If the upper bound lies below 10 msec, ICH E14 deems the study a ‘negative study,’ a result associated with no (less) regulatory concern. If the upper bound lies at or above 10 msec, the study is deemed ‘positive,’ a result associated with regulatory concern. However, regulatory interpretation of the results of a TQT study is more subtle than the previously mentioned dichotomous terms ‘negative’ and ‘positive’ suggest. A result for QT/QTc interval prolongation of 10.1 msec does not automatically mean that the drug will not make it to market. The greater the degree of QT/QTc prolongation, the greater the regulatory concern, and a positive study means that the sponsor may be expected to conduct more extensive and intensive cardiac monitoring in later Phase III clinical trials than would typically be the case for a drug of that class. It should be noted, however, that it is also the case that the greater the severity of the drug’s indication, and the fewer available treatments there are, the more likely a drug is to be approved for a given degree of QT/QTc prolongation (though risk management strategies may be required in drug labelling for drugs with higher risk of QT/QTc prolongation). That said, sponsors would still prefer to see an upper limit of less than 10 msec when they conduct their TQT study.

Powering a TQT Appropriately: Optimum-quality Research Methodology and Sample-size Considerations
Sample-size estimation is a statistical process by which a research group decides how many subjects to include in a given clinical trial, which can also be expressed as the size of the trial. Researchers wish a clinical trial to be powerful enough to achieve its goals, and it is generally regarded that a study should be as powerful as practically feasible.

In a straightforward hypothesis test of the efficacy of a new drug, the efficacy treatment effect will be defined as the mean change in the drug treatment group minus the mean change in the control treatment group (active control or placebo). The researcher’s goal is to power the study such that, if the drug is truly efficacious, a statistically significant treatment effect will be seen. By comparison, for the TQT study the researcher’s goal is to power the study such that, if the drug truly does not prolong the QT/QTc interval to a degree that warrants regulatory concern, the study will successfully demonstrate this. To do so, the upper bound of the one-sided 95% CI placed above the treatment effect point estimate must fall below 10 msec. Three factors influence whether the upper bound will fall below 10 msec:

• The magnitude of the treatment effect point estimate: the closer the point estimate to the threshold of 10 msec, the greater the likelihood of the upper bound falling at 10 msec or above.
• The amount of variation in the individual subjects’ data: the greater the individual variation, the further from the point estimate the upper bound will lie, and hence the greater its likelihood of falling at 10 msec or above.
• The number of subjects in the trial: the greater the number of subjects, the greater the precision in the point estimate, and hence the lesser the upper bound’s likelihood of falling at 10 msec or above.

With regard to the first bullet, if we have evidence that the mean QTc prolongation is 1 msec, a small study could suffice to rule out the 10 msec threshold. On the other hand, if a prolongation of 8 msec has been consistently evident in previous studies, a relatively large study will be needed to exclude 10 msec.

Consider now the second bullet point. It follows from the information provided that decreasing variability is a highly desirable goal. This goal falls within the province of employing optimum-quality research methodology. In biological systems, intrinsic neural and physiological variation makes a certain degree of variability in biological parameters and responses unavoidable. A given subject’s QT intervals will vary to a certain degree from heartbeat to heartbeat, even when the subject is drug-free and lying as relaxed as possible in a quiet, controlled environment. This variation is referred to as intra-subject variation. Taking multiple readings in a given timeframe of interest and then averaging them is a well-documented way of reducing variation, with triplicate measurement offering a good balance of statistical control and cost12. Maintaining a controlled environment for all subjects and treating them in precisely the same manner (to the extent possible) throughout the study will minimise inter-subject variability, the difference between subjects, and also help to minimise intra-subject variability.
Consider now the third bullet. Having a large enough number of subjects is a desirable goal. However, increased sample sizes are accompanied by increasing costs and timelines. An important question for the sponsor to consider is: How can the TQT study best be designed such that, if the drug truly does not have a QT/QTc prolongation liability of regulatory concern, compelling evidence of this is provided by the study? The precise definition of ‘best’ can vary from sponsor to sponsor and drug to drug, but in general terms it would mean having a comfortably high likelihood of providing the desired compelling evidence in the most resource-efficient manner, where both cost and time factor into this equation. A central component of the study design is choosing the number of subjects that need to participate.

Cost Considerations
If a sponsor has little or no ECG data from which to inform this choice, the conservative approach is to use a larger number of subjects. However, this choice can be meaningfully informed by conducting rigorous ECG and hence QT/QTc assessments in early-phase trials. It is certainly true that conducting triplicate ECGs (the recommended strategy for TQT studies) will lead to an additional cost compared with single readings (one ECG reading per timepoint of interest). However, it is possible that the savings from using these data to more optimally design a subsequent TQT test could be considerable, easily outweighing the increased early-phase costs. A good initial understanding of the degree of drug-induced QT/QTc prolongation, and also the variability in such prolongation seen among subjects, will allow the TQT to be designed with the minimum necessary number of subjects, leading to a less expensive and shorter study and hence a shorter overall clinical development programme.

Such a potential saving occurs should the sponsor make a “go” decision following completion of the early-phase studies. An added benefit (a fail-safe) of this approach occurs if the only other decision that can be made at that point, i.e., a “no-go” decision, is made on the basis of unacceptable evidence of the drug’s likely true QT/QTc prolongation liability. That is, the no-go decision occurs earlier than it would have done had the similar decision been made later in the clinical development programme following the conduct and analysis of the TQT study, hence again saving time and money. In either scenario, therefore, the odds of saving time and money are in the sponsor’s favour when choosing to conduct rigorous ECG and hence QT/QTc assessment in the drug’s early-phase clinical programme. Detecting QT/QTc liability even before proof-of-concept studies, therefore, can save considerable resources.

QT/QTc Assessment in Early-phase Studies
Many sponsors have now started modifying QT/QTc assessment strategies in their Phase I studies. In a typical drug development programme, early-phase studies include single ascending dose (SAD) studies, multiple ascending dose (MAD) studies, steady state studies, drug and food interactions studies, special population studies, and pharmacogenetic studies if required. Cardiac safety assessment has not historically been the primary objective of these early human studies, with sponsors typically recording paper ECGs at a few timepoints in Phase I studies for subject safety reasons, i.e., the principal investigator determining if there are clinical indications that the subject should be withdrawn from the study. However, with a small but important amount of modification in the research methodology employed, these studies provide an excellent opportunity for systematic initial QT/QTc prolongation assessment.

Employment of the same well-controlled environment and recording ECGs with the same stringent quality control that is required in the TQT study is certainly feasible during SAD and MAD studies. A standardised approach employing recording of high-resolution digital ECGs and blinded ECG analysis using a core ECG laboratory will considerably reduce variance in QT interval measurements, thereby improving the power of these studies that have small sample sizes. To provide the most useful information regarding QT/QTc prolongation effects, the sampling timepoints of ECGs should be well adapted to the drug’s predicted pharmacokinetic profile, and the ECG assessment should be conducted according to a rigorously standardised procedure. Use of continuous (Holter) recordings has many advantages. First, it permits subsequent extraction of ECG snapshots at timepoints close to Tmax (and hence close to Cmax) should the observed Tmax differ from the predicted one. Second, many more replicates of 10-second ECG snapshots can be extracted at multiple timepoints to provide a large number of data points to mitigate the disadvantage of small sample sizes in early-phase studies. Third, any number of additional ECGs can be extracted post-hoc for further analysis. Fourth, ECGs can be extracted at a stable heart rate, thereby eliminating the confounding effect of hysteresis in the heart rate–QT relationship.

With regard to study design enhancements, a typical SAD or MAD study could be modified to add a Day -1, where time-matched ECG measurements are obtained following placebo administration a day prior to administration of the study drug. This would further improve the power of the study as this design would yield considerably lower variability for assessment of QT prolongation relative to that used in the analysis of conventional SAD and MAD studies through the use of within-subject rather than between-subject variability (such a reduction may be in the order of 33%, from 12 msec to 8 msec). Moreover, this would also permit estimation of individual placebo-adjusted drug-induced QT/QTc prolongation.

Another advantage conferred by this early-phase QT/QTc investigational strategy focuses on the fact that these studies are designed to find the drug’s MTD. Therefore, they provide an opportunity to study the QT/QTc interval effects at doses higher than those eventually studied in a TQT study, i.e., the proposed therapeutic dose and the chosen supratherapeutic dose. Moreover, duration of the MAD study frequently covers the pharmacokinetic profile of all known as well as subsequently identified metabolites, which may themselves have an effect on the QT/QTc interval.

Content of an Integrated Cardiac Safety Portfolio
As captured by the title of this paper, data from early-phase clinical trials can meaningfully contribute to a drug’s Integrated Cardiac Safety Portfolio. At the time first-in-human (FIH) clinical trials commence, such a portfolio should already exist, comprising all relevant nonclinical data: Those data best inform FIH study design. It is then appropriate to add
data from all phases of preapproval clinical trials so that the portfolio can be presented along with all other information filed in a new drug application, in the same way that a (general) Integrated Summary of Safety will be presented.

At the time a sponsor submits a dossier to a regulatory agency requesting marketing permission, the Integrated Cardiac Safety Portfolio will contain nonclinical data, the early-phase data discussed in this paper, and data collected in (subsequent) Phase II studies, a TQT study, and Phase III trials. (Subsequent information will be added from Phase IV trials and postmarketing surveillance if the drug receives marketing approval.) As noted earlier, regulators do not reflexively determine that the upper bound of a one-sided 95% CI from a TQT study of slightly greater than 10 msec means that the drug will not be approved for marketing. Rather, their degree of regulatory concern will have determined how extensively and intensely cardiac monitoring was conducted in Phase III clinical trials. Therefore, with the exception of determination of unambiguous evidence of an unacceptable QT/QTc prolongation liability, and hence a terminated programme, the portfolio will contain cardiac safety information from all phases of preapproval clinical investigation.

A corollary of this comprehensiveness is that it is advisable for one individual (or a small group of individuals) at a sponsor organisation to be involved in the assembly and review of the portfolio throughout the clinical development programme. It is also advisable that, to the greatest extent possible, the sponsor ensure consistent methodological implementation and ECG acquisition and analysis throughout all studies. Such approaches facilitate a truly integrated approach to cardiac safety throughout the development programme.

Concluding Remarks

The incorporation of intensive ECG and hence QT/QTc monitoring in early-phase clinical studies confers financial benefit to the sponsor, whatever the result of this assessment. Either the sponsor gets information that leads them to terminate the compound before spending considerable more money only to get the same information following the completion of a subsequent TQT study, or they get information that enables them to better design their TQT study in due course. This approach therefore offers double protection from an accidentally "penny-wise-and-dollar-foolish" clinical development strategy. Additionally, it affords the sponsor the opportunity to move toward the commencement of Phase III trials more expeditiously, since a better designed TQT study containing the minimum necessary number of subjects can be completed in less time, and less expensively, than an unnecessarily larger study. Better study design also yields a more informed selection of doses for subsequent evaluation.

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Journal for Clinical Studies 31