Assessing proarrhythmic potential of drugs when optimal studies are infeasible

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Assessing the potential for a new drug to cause life-threatening arrhythmias is now an integral component of premarketing safety assessment. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline (ICH) E14 recommends the "Thorough QT Study" (TQT) to assess clinical QT risk. Such a study calls for careful evaluation of drug effects on the electrocardiographic QT interval at multiples of therapeutic exposure and with a positive control to confirm assay sensitivity. Yet for some drugs and diseases, elements of the TQT Study may be impractical or unethical. In these instances, alternative approaches to QT risk assessment must be considered. This article presents points to consider for evaluation of QT risk when alternative approaches are needed. (Am Heart J 2009;157:827-836.e1.)

Regulatory authorities from Europe, Japan, and North America coordinate scientific and technical aspects of drug regulation via the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The mission of ICH is to promote economic efficiency and rapidity of pharmaceutical development without sacrificing quality, safety, or efficacy. A series of ICH Guidelines provides consensus advice regarding these issues. Guideline E14, (Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs) describes evaluation of drug-induced QTc prolongation via a controlled clinical study, the Thorough QT (TQT) Study.

Guideline E14 acknowledges that not all drugs are appropriate for TQT testing. First, drug toxicity at times precludes testing in healthy volunteers (HVs) or at the supratherapeutic study drug exposures recommended for the TQT Study. Second, TQT studies in study subjects with diseases to be treated by a study drug may be infeasible if need for treatment precludes placebo treatment or crossover study design. Finally, comorbidities and concomitant medications in patients can confound QT assessment results. Given these challenges, acceptable alternative approaches to evaluation of drug-induced QT prolongation would facilitate development of new drugs to treat serious and life-threatening diseases.

An essential goal of the Food and Drug Administration (FDA) Critical Path Initiative (CPI) is to foster an appropriate balance between government regulation and the public health benefit that accrues from FDA oversight of drug development and marketing authorization. Based on CPI principles, the Cardiac Safety Research Consortium (CSRC) was developed to foster collaborations among academicians, industry participants, and regulators that address cardiac safety issues relating to development of new medicines (www.cardiac-safety.org). A CSRC subgroup was established to foster stakeholder discussion about QT risk assessment for drugs when a TQT Study is infeasible. This article presents a collaboration of regulatory, academic, and industry discussants. We summarize areas of emerging consensus regarding reasonable approaches to clinical QT risk assessment, conundrums for which consensus remains elusive, and suggestions for additional research. Appendix A, available online, distills this summary.

Drug sponsors in North America are encouraged to review their plans for QT evaluation with regulatory

authorities early in a product's clinical development. Premarketing QT risk assessment should consider the following 5 elements:

1. Available preclinical information, including chemical class of the study drug.
2. The most robust feasible clinical assessment of QT risk, given study drug and disease risk profiles.
3. Analysis of any QT interval-related adverse events reported during clinical development.
4. Summary analysis of overall QT risk profile, taking into account all available data.
5. Risk minimization when QT prolongation is a clinically relevant problem.

This information is collated in the New Drug Application and determines appropriate labeling of QT risk, as well as need if any for a QT-related postmarketing requirement. Although FDA's interdisciplinary review team for QT studies provides expert assessment and advice concerning QT-related issues, jurisdiction for decisions regarding study drug safety and efficacy remains with therapeutic area review divisions.

QT safety

The electrocardiographic (ECG) QT interval represents the time from initiation of ventricular depolarization to completion of ventricular repolarization. This interval varies with heart rate, autonomic tone, age, sex, and time of day.[1] Corrected QT (QTc) is the QT interval corrected in one of several ways for heart rate. Prolongation of the QT/QTc interval has been associated with development of a cardiac arrhythmia known as *torsades des pointes* (TdP). Torsades des pointes means "twisting of the points" and refers to observed waveform amplitude twisting of the ECG around an isoelectric point of QRS complexes. This arrhythmia can revert spontaneously into a sinus rhythm or degenerate into ventricular fibrillation. The latter usually leads to sudden cardiac death.[2] The TdP risk increases with extent of QT prolongation although this relationship is difficult to quantify at mild to moderate levels of QT prolongation. Because of TdP's potential sudden lethality, QT prolongation has become a major focus for drug safety.

Terfenadine's history provides a paradigmatic example. This first-developed nonsedating antihistamine, approved for use in 1981, was initially reported to cause symptomatic TdP 9 years later. The affected patient was taking the labeled dose of terfenadine, as well as ketoconazole.[3] Parent terfenadine is normally present at low concentrations due to rapid conversion by cytochrome P450 enzyme 3A4 to an active metabolite, fexofenadine. Ketoconazole strongly inhibits 3A4, leading to greatly increased exposure to the parent drug, which causes QT prolongation.[4-6] Additional TdP cases were observed in patients taking terfenadine in settings that increased drug exposure (liver insufficiency and overdose) or susceptibility to QT prolongation (congenital long QT syndrome and concomitant QT-prolonging medication).[7-10] Later, terfenadine was shown in vitro to block the delayed rectifier current (I_{Kr}) potassium channel, providing a molecular mechanism for the observed QT effect.[11] Terfenadine was removed from the US market in 1997.[12] Regulatory experience with terfenadine, as well as astemizole and cisapride, led an ICH expert working group to advocate standards for premarketing evaluation of a new study drug's propensity to cause clinical QTc prolongation.

Preclinical QT risk assessment

The ICH Guidelines S7A and S7B describe preclinical assessment of QT prolongation. Preclinical safety pharmacologic studies are commonly performed before first-in-human testing to provide an indication of a study drug's likely clinical QT risk. Pharmacologic characterization of the study agent in animals may further reveal circumstances in which increased drug or metabolite concentrations might raise QT safety risk in humans. Knowledge gained from preclinical studies can be used to develop an early risk profile and to plan appropriate ECG monitoring during clinical development. For example, a compound that demonstrates a significant preclinical effect on QT prolongation may lead the sponsor to undertake more frequent, replicated, manually adjudicated ECG monitoring in early clinical studies until the potential risk is characterized. Finally, in settings when a standard TQT Study cannot be performed, regulatory authorities may place increased reliance on nonclinical study data.

Guideline S7B recommends in vitro testing of drugs for effects on I_{Kr}. Of 5 potassium ion channels in the cardiac myocyte membrane, I_{Kr} is the one responsible for most instances of drug-induced QT prolongation.[13] Potassium ion flux through I_{Kr} is measured using a cell line engineered to express the cloned ion channel gene *hERG*.[14] The ICH guidelines also recommend testing for a compound's effects on the ECG in a nonrodent study. Such in vivo ECG studies integrate effects of the study drug on all cardiac ion channels, not just I_{Kr}. Similarly, evaluation of the cardiac action potential in dog or rabbit heart Purkinje fibers provides integrated information on cardiac ion currents beyond I_{Kr} alone. Finally, isolated Langendorff heart or ventricular wedge preparations can be used to assess potential of a compound to prolong repolarization and induce arrhythmia.[15] Hysteresis refers to delayed equilibration between plasma drug concentration and QT effect. Its causes include distributional delay, active metabolites, and altered ion channel trafficking. When QT prolongation is observed after prolonged but not short-term exposure, ion channel trafficking assays may be informative regarding

mechanism. Hysteresis, due in part to altered ion channel trafficking, is characteristic of the QT effect produced by arsenic trioxide.[16]

Comparison of hERG and/or nonrodent study results with anticipated free plasma concentration in humans predicts incompletely the clinical QT effect.[17-19] Nonetheless preclinical studies have high positive predictive value for clinical QT prolongation risk. When preclinical assessment raises concern for QT prolongation, early clinical development should explicitly consider study subject safety and characterization of the exposure-toxicity relationship of clinical QT effect.

By contrast, when preclinical studies are performed and show no evidence of QT effect, concern for possible clinical proarrhythmia persists. Confounding factors in preclinical assays include inadequate power to detect a modest drug effect, absent confirmation of assay sensitivity, and inadequate blinding. However, the reasons for documented failures of these tests to predict human QTc prolongation remain unclear. Insufficient negative predictive value of the battery of preclinical assays for clinical QT risk has led the FDA and Health Canada to consider negative preclinical assessment to be inadequately reliable to exclude clinical QT risk. Thus the TQT or an alternative clinical QT evaluation remains the cornerstone for exclusion of clinical QT risk.

The TQT Study

Guideline E14, finalized in May 2005, addresses QT interval safety evaluation. This Guideline recommends that most new and some marketed compounds undergo clinical ECG evaluation to assess potential for QT prolongation. To exclude drug-induced QT risk, ICH E14 advocates use of the Thorough QT/QTc (TQT) Study design. The TQT design's rationale is that even modest mean QT prolongation in HV demands more attention to risk evaluation in larger, heterogeneous populations studied in phase 2 and 3 trials, including individuals with predisposing high-risk conditions or genetic abnormalities affecting cardiac repolarization. Doses studied in a TQT Study should reflect the highest expected potential drug exposures that could occur due to drug-drug interactions, metabolic compromise, or overdose.

The TQT Study provides for a hypothesis testing, controlled experiment that is considered best practice for clinical QT risk assessment. In a TQT Study, the subjects (usually HVs) receive separate administrations of placebo, a positive control drug that causes modest yet reliable QT prolongation, and study drug at maximal therapeutic and supratherapeutic exposures. Electrocardiograms are collected with time-matched data acquisition to control for diurnal variation in QTc interval. As described in ICH E14, testing is generally performed in HVs taking no other medications and having no other potentially confounding factors.

The ICH E14 paradigm assumes that mean maximal QT prolongation <5 milliseconds implies a minimal TdP risk, whereas above this threshold, there may be an elevated risk of proarrhythmia in a large, heterogeneous population. A TQT Study measures mean change compared with placebo in time-matched QTc interval between baseline and multiple postdose time points. Analysis intends to determine with 95% confidence that the true maximal effect is <10 milliseconds. The null hypothesis, H0, is that "there exists a QT effect." The alternative hypothesis, H1, is that "there does not exist a QT effect."

Null hypothesis and H1 can be written more specifically as follows:

$$H0 : \text{Max}_k(\Delta\Delta QTc[t_k]) \geq 10 \text{ milliseconds versus}$$
$$H1 : \text{Max}_k(\Delta\Delta QTc[t_k]) < 10 \text{ milliseconds for } t_1, t_2, \ldots, t_K,$$

where $\Delta\Delta QTc(t_k) = \mu_T(t_k) - \mu_P(t_k)$ is the mean difference in baseline-adjusted QTc at time t_k for treatment and placebo groups. A concurrent positive control study drug with known modest QT-prolonging effect is included to confirm the study is sensitive enough to detect a study drug QT effect of interest when one exists.

QT safety of anticancer products

The level of acceptable risk from a therapy depends on the nature and magnitude of its risks, as well as the risks and benefits of alternative therapies. Where clinical benefit is substantial, considerable QT prolongation may be acceptable. Arsenic trioxide, for example, is approved in the United States for treatment of acute promyelocytic leukemia and retains marketing authorization despite its recognized propensity to cause clinically significant QT prolongation.[16] When a clinical QT effect is established, magnitude of risk in clinical use should be characterized to inform prescribers and support appropriate risk minimization.

Even when a net clinical benefit can be assured, it is important to characterize risks for which a risk management strategy can optimize clinical benefit. For example, myelosuppression caused by cytotoxic chemotherapy drugs is mitigated by monitoring hematologic effects. Similarly, leukemia specialists have adopted QT risk management to address the proarrhythmic risk after administration of arsenic trioxide. Risk management will be described in greater detail later.

In development and registration of anticancer drugs to treat advanced disease, regulators have accepted departures from formal, E14-type TQT analysis to characterize QT risk in circumstances when a standard TQT Study cannot be performed for safety or ethical reasons.[20] Nonetheless, the rationale for each departure from the ICH E14-defined QT risk assessment paradigm should be stated explicitly to justify the next best alternative analysis plan. Several factors limit universal application of

Table I. Thorough QT Study design consideration for anticancer drugs

TQT feature per E14	Oncology study feature	Implication for QT risk evaluation
HVs	Genotoxin; tolerability	No HVs
Supratherapeutic exposure required	Presumed therapeutic exposure at maximum tolerated dose	No supratherapeutic exposure
Positive control drug	Advanced refractory cancer populations	Consider 5 HT-3 inhibitor as positive control or no positive control as appropriate
Time-matched ECGs; use of placebo and washout period without active treatment	Advanced refractory cancer populations	Extended placebo dosing and washout not acceptable

Table II. Exposure-response study designs for QT risk testing

Trial design	Features
First-in-human phase 1a adjunct	Baseline time-matched to on-therapy ECGs if possible
	ECGs collected at all dose levels
	Replicate ECGs, eg, ≥3 for ≤4 min, at each time point
	ECGs taken just before PK sample collection
	At least 4 time points, more if possible, guided by PK profile
	Manual overreads of ECGs if analysis indicates prolongation
Phase 1b-2 adjunct	Yields more data at MTD
	Typically at least 4 time points guided by PK profile
	PK better known so easier to time ECGs
	Patient management better understood
Phase 3 population-PK analysis	Substudy at therapeutic dose
	1-4 PK samples per patient
	ECG samples just before PK sample collection(s)
	Uses all available data
	Reduces cost if development stops before phase 3
	Focus on QT outliers and arrhythmic events

the TQT Study design for some anticancer drug development (Table I). Study products may not be given safely to HV at presumed therapeutic doses, for example, based on known genotoxicity or dose-limiting tolerability. Investigational anticancer drugs administered at maximum tolerable doses cannot be tested safely at supratherapeutic concentrations, even in cancer patients. Patients with refractory malignancies and expected survival of weeks to months, for example, those with acute leukemias or advanced solid tumors, could justifiably be excused from the burden of time-matched baseline ECG values and separate administration of a positive control.

Concentration-QTc modeling

Use of pharmacometric methods is well established in drug development.[21,22] For characterizing a known clinical QT risk, understanding the relationship between drug concentration and QT interval provides important information.[23,24] In this circumstance, regulatory decision making can be supported by dose and concentration-QTc (CQT) relationships. Such exposure-response analysis entails collection of ECGs at multiple time points on the pharmacokinetic exposure curve. This approach can be applied as a secondary safety end point at any phase of clinical drug development (Table II). Concentration-QTc modeling may have particular value during first-in-human dose-escalation studies when high-quality ECGs and correlative pharmacokinetics (PK) testing can be routinely obtained, even across multiple treatment centers.

Mixed effects modeling may be particularly useful for evaluating the relationship between plasma drug or metabolite concentration and time-matched, baseline-adjusted drug-placebo difference in QTc interval. Most relevant is not mean QTc change but rather distribution in QT and PK variability. Maximum mean change is less

informative when PK is highly variable. For example, mean overall QTc change after ranolazine administration is 6 milliseconds, but in the 5% of patients with highest plasma concentrations, mean QTc prolongation is at least 15 milliseconds.[23] Exposure-response modeling can also help to differentiate effects of high drug concentration versus differential susceptibility of a patient subgroup to an adverse event.

Exposure-response analysis is not generally used for hypothesis testing. In some circumstances, different investigators can reach different conclusions with the same dataset. Modeling may give biased estimates of drug-induced QT interval prolongation if model assumptions are not correct. Thus diagnostic evaluation is expected as part of exposure-response method application. The most efficient approach to CQT modeling is ECG collection from as many treated patients as possible, especially in phase 1 dose-escalation studies when QT data can be collected in a controlled setting under low and high achieved serum concentrations.

Clinical study QTc thresholds

Clinical QTc thresholds for study eligibility, dose modification, or discontinuation should be tailored to an investigational drug's risk-benefit profile for the intended disease treatment indication, as well as the feasibility of discharging or characterizing extent of QT risk at that point in clinical development. Consideration of QT risk should balance patient safety with desired access to

Table III. QTc-related adverse events by CTCAE, version 3.0

Grade	Severity	QTc definition (ms)
1	Mild	>450-470
2	Moderate	>470-500 or increase by ≥60
3	Severe	>500
4	Life-threatening	>500 with life-threatening signs or symptoms of TdP
5	Fatal	

Data from http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf.

potentially effective new therapy in the setting of alternative treatment. For patients with refractory cancer, risk of death from malignancy may substantially exceed likelihood of drug-induced TdP, even if drug-induced clinical QT risk is present.

Common Terminology Criteria for Adverse Events (CTCAE), version 3.0, is widely accepted as a de facto standard for describing and managing safety findings in clinical studies of anticancer therapy.[25] Table III provides CTCAE categorization of QTc prolongation. Observed absolute QT/QTc values >500 milliseconds, that is, grade 3 in the CTCAE framework, are commonly considered a relevant threshold of concern.

Eligibility

The normal QTc interval in adults has an estimated mean of about 400 milliseconds and upper limit of 440 to 470 milliseconds.[1] Guideline E14 recommends an upper limit of 450 milliseconds for subjects in clinical trials until effect of the drug on QT/QTc interval has been characterized. Although published data remain sparse,[26] results from a small study suggest that up to 15% of patients with advanced cancer exhibit baseline QT intervals >450 milliseconds. This finding is consistent with common use of concomitant QT-prolonging medications and the observed higher distribution of QTc values correlated with advancing age >50 years.[1] In the setting of life-threatening disease, use of ICH E14 QT eligibility thresholds could result in inappropriate exclusion of patients from clinical studies of potentially effective drugs. For such diseases, a baseline QTc exclusion criterion of >470 milliseconds, that is, not exceeding National Cancer Institute CTCAE grade 1, may be more suitable. In studies of advanced refractory cancer without established treatment alternatives, some investigators have used even more flexible eligibility, enrolling patients with QTc up to 500 milliseconds. When appropriate, these more flexible eligibility criteria can be coupled with additional ECG monitoring and other strategies for risk minimization.[27,28]

Dose modification or discontinuation

Guideline E14 notes commonly used clinical study treatment discontinuation thresholds of QT/QTc

>500 milliseconds and increase from baseline of >60 milliseconds. Nonetheless, E14 recommends that thresholds for each trial be based on risk tolerance considerations appropriate for the indication and patient population studied. Depending on the benefit-risk profile of an anticancer drug and its intended treatment indication, the following alternative approaches have been used:

1. Use of averaged QTc values obtained from replicate ECG collection to reduce QT measurement variability at individual time points.
2. Manual adjudication of measured QT prolongation.
3. Risk minimization, that is, electrolyte supplementation and enhanced ECG monitoring.
4. Dose reduction instead of discontinuation if QT reaches a threshold of concern.
5. Dosing "holiday" to document QTc normalization, followed by re-treatment at same dose level coupled with additional ECG monitoring and risk minimization.

Many risk factors for TdP apply broadly, including active ischemia, congestive heart failure, electrolyte abnormalities, concomitant QT-prolonging medicines, and family history of sudden cardiac death before age 40 (a potential predictor of congenital long QT syndrome). Given a study product with known QTc risk from preclinical assays, such TdP risk factors would be appropriate exclusion criteria for studies in disease indications where imminent risk of death is low and safe effective treatment alternatives exist. For investigator convenience, a list of QT-prolonging medicines could be provided in the clinical study protocol, for example, as provided on www.QTdrugs.org. Normal QTc interval in females tends to be slightly longer than that of men (up to 470 milliseconds), so criteria could also be tailored to sex. Finally, an additional 20 to 30 milliseconds should be added to inclusion and discontinuation criteria if a patient has preexisting bundle branch block.

Ideally, there should be a minimum 50 to 60-millisecond difference between the upper limit of eligibility and lower limit of discontinuation or treatment modification. This threshold of change is consistent with both E14 and CTCAE. Nonetheless, normal diurnal variability of QTc in HVs can be 70 to 90 milliseconds.[29,30] Thus, differentiation of a drug's QT-prolonging effect from effects of normal diurnal variation, comorbidities, or other medications may be difficult without time-matched ECGs. Replicate ECG readings are useful to reduce variability of individual QT interval measurements. Furthermore, if absolute QTc remains in an acceptable range in the setting of a measured 60-millisecond QTc increase from baseline on study drug, risk-based options could include increased ECG monitoring and/or control of TdP risk factors such as electrolyte abnormalities, with or without dose reduction. Alternatively, if time-matched ECGs are

not collected, then consideration could be given to deemphasizing changes from baseline as a criterion for treatment modification or discontinuation. In these situations, absolute QTc alone, for example, CTCAE grade 2 or 3, may be acceptable for monitoring and managing interventions to manage proarrhythmic risk.

Electrocardiographic data collection

Twelve-lead ECGs enable accurate measurement of the QT interval and are likely to be adequate in most instances for QT evaluation during drug development. The ECG data collection to assess clinical QT risk should include the following 4 elements:

1. ECG machines should be validated to ensure collection of high quality data.
2. ECG data collection should be digital, especially when refined quantitative analysis of QTc is an explicit study end point.
3. Replicate (preferably triplicate) ECG collection should be obtained at all time points to reduce noise of individual QT interval measurements.
4. Both fully manual and manual adjudication of automated QTc interval measurement are considered more reliable for QT interval measurement than fully automated methods. Alternatively, automated QT measurements performed early in clinical development could be reanalyzed by manual adjudication later in a central laboratory if warranted by a decision to advance the study drug to full development.

Fully automated ECG interpretation in a TQT Study was reported in HV to generate less variability than manual QT assessment and to yield mean results close to those of manual ECG reading.[31] However, outlier analysis may differ significantly between manual and automated reading. Typically, when fully automated QT measurement errs, noise or artifact at the end of the T wave is included in measured QT interval and can lead to a false-positive signal for QT risk. Oncology and other morbidly ill patients may have prominent ST/T wave abnormalities and baseline artifact that can interfere with machine interpretation of the QT interval.

Analysis of outliers

Categorical analysis of QT interval prolongation and/or arrhythmia observed at any stage of clinical development may reveal cardiotoxic effects of the study drug. However, false-positive signals might be more common in patients, as opposed to HVs participating in a TQT Study. Comorbidities, medications, and electrolyte abnormalities causing QT prolongation should be considered for each individual patient outlier before concluding that a study drug-induced QT prolongation. In addition, patients

with borderline high baseline QT values may be more likely than others to display QT prolongation due to normal diurnal variation of QTc. Any of these factors may confound analysis. In such instances, changes from baseline may better define a significant drug effect. Considerations should include measures of central tendency, categorical analysis of outliers, and summary interpretations of abnormal ECG findings.

Statistical analysis

Summary analysis of QT prolongation risk should consider components listed below. In practice, some of these safety measures are difficult to interpret in the absence of randomized studies. Categorical analyses that use CTCAE, version 3.0, severity grades for QTc prolongation may be especially informative for product labels because this nomenclature is in standard use by most oncologists for describing treatment toxicity.

1. Measures of central tendency: mean absolute and baseline-adjusted heart rate, as well as, RR, QT, QTc (QTcF, QTcB, and other QTc correction formulae), PR, and QRS intervals for each assessment time point, including 2-sided 90% CIs, as well as mean maximum absolute and baseline-adjusted values for each parameter.
2. Categorical analysis: number and percentage of individuals with absolute QT/QTc values >450 milliseconds, >480 milliseconds, and >500 milliseconds and number and percentage of individuals with changes from baseline >30 and >60 milliseconds.
3. Number and percentage of individuals with abnormal ECG findings.
4. Number and percentage of individuals with adverse events that could be associated with prolongation of cardiac repolarization or proarrhythmia, that is, palpitations, dizziness, syncope, cardiac arrhythmias, and sudden death.

Given that many drugs and disease states affect heart rate, it is important to ensure that an appropriate QT correction formula is used. Scatterplots of QTc versus heart rate relationships can demonstrate suitability of the correction formula, that is, one that generates slope of QTc versus HR as close to zero as possible.

Timing of clinical QT risk assessment

Early human testing may appropriately proceed to registration studies without establishing full knowledge of dose and schedule considerations. Similarly, management of diverse toxicities may not be well described for drugs until late in clinical development or postapproval. Yet knowledge of these features will affect optimal design and conduct of QT studies, particularly in patients with advanced malignancy. Therein lies the conundrum for

study drug sponsors. On one hand, a dedicated QTc evaluation study may be optimally conducted later in drug development when pharmacology, risk management, and concomitant supportive care issues are better characterized.[32] On the other hand, early QT evaluation can inform appropriate risk minimization for later trials.

QT risk assessment during clinical drug development presents an inherent challenge relative to development timelines. The optimal opportunity to collect a robust dataset may be during early clinical study of a study drug's PK, particularly in situations when a standard ICH E14 TQT cannot be performed. Characterizing CQT relationship in an early phase study can improve efficiency of drug development by alerting the sponsor to a potential QT effect before performance of a dedicated QT study. In this setting, digital ECG collection can be timed to precede blood sample collection for PK analysis. On the other hand, rigorous ECG collection and analysis in phase 1 incurs costs that may be unneeded for a class of study drugs characterized by a high failure rate in early clinical development. Some sponsors have pursued rigorous ECG collection with automated ECG interval measurements during first-in-human dose escalation using methods that also capture and store digital tracings. If development continues, these digital ECGs can be submitted later to a core laboratory for manual adjudication. In this manner, safety evaluations are assured in early clinical studies, whereas expenses are better matched to phase of clinical development.

If results from early development enable characterization of clinical QTc risk sufficient for labeling and risk management of the intended treatment indication, then a separate, dedicated study may not always be necessary or feasible. However, the advantages of conducting a dedicated QT risk study later in development include availability of comprehensive PK information, an established risk management algorithm, and control of comorbidities and medications that can confound QT risk assessment.[32] After first-in-human dose escalation, when maximum tolerated dose and PK are better characterized, ECG collection can be timed more easily to coincide with maximum concentration or other time points of interest. Drug-drug interaction studies may provide an opportunity to estimate the QT effect at high drug exposures likely to occur in larger phase 3 populations exposed to polypharmacy. Finally, when appropriate, a population-PK approach to exposure-response analysis of QT prolongation could be incorporated into larger phase 3 clinical studies. An important caveat to population-PK analysis for QT risk evaluation is that quality controls and other logistic issues might limit feasibility of such studies conducted in multiple centers.

Balancing these considerations needs to take into account each drug's particular profile. When considering these issues, drug sponsors are strongly encouraged to seek feedback from regulators on trial design(s) as early as possible in development. In addition, regulatory authorities encourage sponsors to submit study report(s) for interpretation to confirm agreement between sponsor and regulators on study findings.

Risk minimization

Risk minimization should be considered in the context of efficacy and toxicity of alternative treatments. For example, many drugs to treat life-threatening diseases such as cancer impose safety risks. Such risks are acceptable when outweighed by clinical benefit. Nonetheless, in these circumstances reasonable measures to minimize risk should be embraced.

When available information raises concern for clinical QT prolongation, the following precautions should be considered:

1. Modification of eligibility, discontinuation, and dose modification criteria based on understanding of QT risk and risk-benefit profile of the study drug and disease indication.
2. Exclusion or additional monitoring of patients with TdP risk factors, for example, recent ischemic heart disease, congestive heart failure, or family history of sudden cardiac death before age 40.
3. Substitution or elimination of concomitant QT-prolonging medications when possible.
4. Evaluation of and supplementation of magnesium, calcium, and potassium before drug dosing.
5. Risk-based rules for repeat dosing, additional ECG monitoring, and updated consent after observation of significant treatment-associated QTc prolongation.

Labeling

QT assessment should in general be available at the time of approval. When demonstration of clinical benefit supports drug approval, the product label should provide a summary of QTc evaluations with relevant considerations if any for the indicated treatment population. Positive findings from preclinical and clinical experience can be summarized as a subtitled section in Warnings or Precautions. Available data may also merit discussion in other sections, for example, Highlights, Contraindications, Drug interactions, and Special populations.

Conclusions about QTc liability should be appropriately qualified. For example, language can be added to clarify methods, especially when they diverge from those of a conventional TQT Study. Results of exposure-response modeling should be supplemented by other relevant findings. For example, number and percentage of patients with QTc >500 milliseconds would be clinically informative for patient care. Given sufficient data and technical quality, clinical or preclinical findings that indicate no observed QTc prolongation can be

Table IV. Disease acuteness versus need for E14-like QT scrutiny

			QT evaluation		
			Low	**Medium**	**High**
			Integrated summary of available data	Best available alternative to TQT	E14-like scrutiny
Acuteness of disease to be treated	High	Efficacy in advanced, refractory disease	×		
	Medium	Treatment of metastatic carcinoma		×	
	Low	Long-term chemoprevention			×

Examples. The following hypothetical examples are for illustrative purposes only. This document does not endorse any specific approach. Differences among compounds must be taken into account when approaching QT risk evaluation.

High acuteness disease—leukemic acute blast crisis. For these critically ill patients, logistic barriers may complicate frequent or extensive ECG and PK sample collection. Eligibility could be liberalized given poor prognosis. Triplicate ECGs at 3 time points about 1 hour before study drug treatment might be followed by replicate ECGs at 6 time points covering maximum concentration. Sponsors may be able to justify omission of placebo, positive control drug, and supratherapeutic drug exposure in the study design.

Medium acuteness of disease—metastatic solid tumor. Despite life-threatening illness, these patients may not require treatment with the immediacy of blast crisis. Eligibility might still be liberalized as detailed in text due to low likelihood of proarrhythmia relative to short-term mortality from underlying disease. Time-matched baseline ECGs may or may not be possible; replicate ECGs at multiple time points should be possible. A crossover design with positive control drug may be feasible. Rigorous ECG collection in phase 1 with concentration-QTc modeling might be sufficient to discharge risk.

Low acuteness of disease—adjuvant or prophylactic therapy for resected or high-risk premalignant disease. HV may be appropriate if study drug is shown to be safe. Either modified or E14 eligibility criteria might be appropriate, depending on circumstances. Rigorous baseline and on therapy ECG collection would be expected. Use of placebo, positive control drug, and supratherapeutic exposures may be appropriate, depending on circumstances.

summarized in the label. However, generalizations that convey lack of human risk for QTc prolongation would not be used unless supported by a dedicated study with positive controls to assure assay sensitivity.

Label information on QT prolongation should include guidance if needed to minimize TdP risk. Typically, strategies for risk management used during development can be extended to the product label. Recommendations should balance safety and access to effective medicines. If a drug has been demonstrated to cause clinical QTc prolongation, warnings and precautions concerning risk factors and anticipated interactions with other QTc-prolonging drugs would be expected in labeling to communicate risk of TdP. Product label updates occur as reported safety data or results from additional relevant studies become available. When a study drug's indication is to expand from a life-threatening disease with poor prognosis, for example, third-line metastatic colon cancer, to an indication with better prognosis, for example, adjuvant therapy for colon cancer, then available data should be updated in the context of the new indication's risk-benefit profile.

Future directions

Targeted research could enhance practical strategies for both detection and risk minimization of QT prolongation in cancer drug development. Warehousing ECG data from multiple sources should enable larger studies to characterize the range and distribution of QT (and other ECG) interval information in patients with different morbidities, prior exposure histories, and ages. Such studies to characterize QTc prolongation could have

implications that extend to other populations with serious and life-threatening diseases.

In addition, alternative positive controls for protocol sensitivity could be more fully characterized. For example, single-dose use of 5-HT3 receptor antagonist antiemetics has been suggested as a candidate positive control treatment for QT assessment studies performed in cancer patients.[32-35] Ondansetron, dolasetron, and granisetron have all been implicated in QTc prolongation. QTc prolongation associated with ondansetron has been described in diverse patient populations.[34] Because QTc prolongation produced by these drugs is of relatively short duration, it may be possible to establish sensitivity on a pretreatment day without carryover QTc prolongation that would interfere with study drug evaluation.

Conclusions

Drugs to treat serious and life-threatening diseases frequently generate safety risks. Tolerance of such risks should be based on expected efficacy and alternative therapy. Large QT-prolonging effects are of greatest concern. Nonetheless, QT prolongation risk should be considered explicitly. Development of such drugs does not preclude need for the most thorough feasible evaluation of QT risk allowable by safety and ethical considerations.

QT risk evaluation should be based on 2 key principles. First, because precautions can mitigate risk, best available methods should be used to characterize magnitude of clinical QT prolongation. Second, overall risk-benefit considerations for a study drug and treatment indication in some instances justify lowering the resolving power of QT assessment. Hypothetical examples for anticancer therapy are provided in Table IV.

Risk minimization should be considered throughout development to improve patient safety both before and after drug approval. When investigational anticancer agents have promising activity, development programs should seek to balance management of arrhythmia risk with preservation of access to potentially beneficial study treatment at bioactive exposures that support the opportunity for disease control.

Disclosures

Views expressed herein may not necessarily represent policies of the Food and Drug Administration or Health Canada.

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Appendix A

POINTS TO CONSIDER FOR QT RISK ASSESSMENT OF DRUGS

TO TREAT SERIOUS AND LIFE THREATENING DISEASES

A. Analysis

1. Premarketing clinical QT risk evaluation should occur regardless of study drug class.

2. The TQT is optimal for exclusion of clinically significant QT prolongation.

3. When a TQT is not feasible, a study drug's characteristics and intended use influence the best alternative approach for assessment of QT risk.

4. If clinical QT prolongation risk is detected, its magnitude should be evaluated.

5. Concentration-QTc modeling facilitates characterization of QT risk magnitude.

B. Operations

1. ECG machine standardization and validation ensure collection of quality data.

2. Digital ECG acquisition reduces noise and increases reliability of QT measurement.

3. Replicate ECG collection reduces variability of individual QT interval measurement.

4. Either manual adjudication following automated measurement or fully manual measurement of QT interval are considered "gold standard" QT risk evaluation.

C. Enduring Challenges in Clinical QT Risk Evaluation

1. Preclinical assessment is not fully validated to exclude clinical QT risk.

2. Concentration-QTc modeling is not a validated method to exclude clinical QT risk.

3. Timing of QT risk assessment during drug development necessitates a trade-off.

D. Future Directions

1. Characterize baseline QT interval and proportion of outliers in acutely ill populations.

2. Validate preclinical assessment model(s) for QT risk assessment.

3. Learn from future experience with concentration-QTc methods for exclusion of clinical QT risk.

4. Evaluate additional agents as positive control drugs for clinical QT risk assessment.