Cardiac Safety Investigations 10 Years after ICH Guidance E14: Evolving Industry and Regulatory Viewpoints on Evaluation of Proarrhythmic Risk during New Drug Development

The year 2015 marks the 10th anniversary of the release of two ICH Harmonised Tripartite Guidelines that have governed the cardiac safety regulatory landscape, more specifically the proarrhythmic cardiac safety landscape,[1] since their release in May 2005. ICH S7B addresses the non-clinical evaluation of the potential for delayed ventricular repolarisation (QT interval prolongation) by human pharmaceuticals,[2] and ICH E14 addresses the clinical evaluation of QT interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs, with a focus on the Thorough QT (TQT) Study.[3,4] Our discussions in this paper focus on clinical evaluations.

Although it has been extremely effective in preventing approval of drugs with QT liability without clear characterisation of their proarrhythmic potential, there has been considerable debate about the need for modifying the current regulatory landscape to focus on earlier QT assessment in Phase I clinical pharmacology studies.[5,6] This paper therefore has several goals. First, the current landscape is reviewed: this is done succinctly since there are already multiple publications in the literature discussing the requirements and consequences of ICH E14 and the associated "Questions and Answers" documents since their release.[7-20] Second, it reviews various professional society activities and publications in the literature that document the background and motivation for an influential Think Tank meeting held on December 12th, 2014, at the US Food and Drug Administration (FDA) Headquarters, Silver Spring, MD, USA, which was attended by representatives from industry, academia, and regulatory agencies from multiple countries. Third, it documents the main results of a prospective study entitled "Can early ECG assessment using exposure response analysis replace the Thorough QT Study?" that were presented at that meeting.[21] Finally, it provides a consideration of the potential ramifications of these results in both the short- and long-term evolution of the proarrhythmic cardiac safety landscape.

Current Clinical Cardiac Safety Requirements

Across the last two decades or so, cardiac safety has been a major concern in the development, approval, and marketing of new non-cardiovascular drugs (drugs not intended for a cardiac or vascular indication),[22] with a substantial number of drugs being restricted in their clinical application or withdrawn from the market due to adverse cardiovascular effects. There were 47 instances of post-marketing withdrawal of drugs between 1957 and 2007; 45% of these were due to concerns regarding cardiovascular toxicity.[23] Similarly, 27% of the potential new drug molecules that failed in the pre-clinical phase in the last two decades did so because of cardiovascular toxicity.[24] Consequently, significant attention has been focused on the prospective exclusion of unacceptable cardiovascular risk during drug development. The level of risk that is deemed 'acceptable' differs based on the disease for which a drug is being developed, the relative severity of the adverse cardiovascular effects, and the availability of safer alternatives.

Among the possible cardiovascular risk liabilities, the risk of drug-induced *torsades de pointes* (TdP), a rare but potentially fatal ventricular arrhythmia, has been a major reason for the withdrawal of licensed drugs, accounting for around 26% of drugs withdrawn from the market between 1990 and 2005.[25] This risk was not identified prospectively during the development of these drugs given the relative rarity of these events and the limited number of clinical trial participants studied in the pre-approval period. However, a common thread which subsequently emerged in these cases was their association with prolongation of the QT interval on the surface ECG. Figure 1 provides a highly-stylised representation of the ECG, the QT interval, and QT interval prolongation.

It was also apparent that these occurrences were concentration-related and almost exclusively linked to delayed cardiac repolarisation due to drug-induced inhibition of the rapid delayed-rectifier potassium current (I_{Kr}), which is the main repolarising current in ventricular cardiomyocytes.[26,27] This I_{Kr} current occurs due to an efflux of potassium ions through the I_{Kr} channel encoded by the human ether-a-go-go-related (hERG) gene, and is therefore also referred to as the hERG channel.[28] It followed, therefore, that the proarrhythmic liability of drugs could be prospectively investigated during drug development by using the QT interval on the surface ECG as a surrogate for their ability to delay cardiac repolarisation. Thus, the current cardiac safety testing paradigm came to be primarily based on the predictive link between drug-induced hERG channel blockade *in vitro* in preclinical studies, QT interval prolongation on the ECG in clinical trials, and the occurrence of TdP when a subsequently approved drug is used in patients.

Since its implementation in 2005, the TQT Study, which has been the cornerstone of clinical assessment of the potential of non-cardiac drugs to cause TdP, has been very successful.[29,30] Not a single drug with unanticipated potential for TdP has entered the market since 2005.[30] However, over-emphasis of this surrogate marker has important limitations and is believed to have adversely impacted the development of potentially valuable therapeutics and increased the cost of developing safe drugs considerably.[31]

The ICH E14 Guidance

In 1997, the Committee for Proprietary Medicinal Products (CPMP) of the European Medicines Evaluation Agency (EMEA, now the European Medicines Agency [EMA]) was the first to issue a regulatory document that highlighted the association between QT prolongation and the increased risk of TdP, and proposed making drug-induced QT prolongation a definitive aspect of cardiac safety testing.[32] This document gave the impetus for deliberation between regulatory agencies, cardiologists, pharmacologists, and statisticians that ultimately resulted in the formulation and release of ICH E14 in 2005.[3]

The TQT study for an investigational drug is usually a blinded, randomised study with four treatment arms – two treatment arms of the investigational drug (the proposed therapeutic dose and a supra-therapeutic dose), a negative control treatment arm (placebo), and an active positive control treatment arm (usually moxifloxacin).[27] The TQT study is designed with the objective of identifying the drug's effect on the QT interval, with a mean placebo-adjusted QTc (QT adjusted for heart rate) prolongation of ≥5 milliseconds (msec) or a one-sided 95 % upper confidence interval of ≥10 msec indicating a QT prolongation risk.[3]

ICH E14 recognises that there can be considerable variability in QT measurement. This is particularly relevant when the threshold of regulatory concern is small i.e., a mean QT prolonging effect of 5 msec. High reader variability also contributes to large within-subject and between-subject variability in QT interval, which in turn increases the calculated sample size of a TQT study. Central ECG laboratories, necessarily, have stringent quality control processes and can maintain high standards of ECG data quality. The ICH E14 guidance, therefore, recommends that ECGs should be read in a central laboratory by a small group of trained readers blinded to treatment, time, and participant identifiers to maintain consistency in QT measurement and to prevent reader bias. Methodological rigour is therefore a critical component of drug-induced QT prolongation evaluation,[33-44] a key point that will be emphasised in a different setting in due course.

Since the implementation of the ICH S7B and E14 guidelines in 2005, the FDA's QT-Interdisciplinary Review Team (QT-IRT) has reviewed and provided advice on over 400 TQT study protocols and over 250 new drug application (NDA) submissions, as well as proposals for ECG monitoring and TQT study waivers.[30] An assessment of the FDA regulatory decisions database for TQT studies between 2006 and 2013 revealed that 46 drugs out of the 205 NDA submissions were identified as QT prolonging drugs.[45] Of these 46 drugs, 41 drugs were approved with appropriate labelling restrictions such as QT-related Boxed Warnings, Contraindications and Precautions, as well as descriptions in adverse reactions, drug interactions, over-dosage, and clinical pharmacology sections of the package insert.[45] Thus, the TQT regulatory approach has made drug safety labelling pertaining to potential cardiac proarrhythmic risk more objective and informative. The most important measure of the success of this approach undoubtedly has been the fact that no new drug approved for marketing after 2005 has been withdrawn due to an increased risk of TdP or sudden cardiac death due to arrhythmias.[30]

One of the limitations of the present ICH S7B-E14 paradigm, however, is that while all drugs which produce TdP prolong the QT interval, not all drugs which block hERG or prolong the QT cause TdP. The current emphasis on hERG/QT prolongation does not take into consideration a compound's effects on other cardiac ion channels which may mitigate proarrhythmic risk. The ICH S7B/E14 approach could have unnecessarily eliminated older drugs like verapamil, which is a potent hERG blocker and prolongs the QT, but is not proarrhythmic due to its effects on calcium currents. Thus, while the current conservative regulatory approach will no doubt protect against the introduction of drugs which may cause TdP, it relies on imperfect surrogates and does not truly assess proarrhythmic risk.

An adverse consequence of this hERG-TQT regulatory approach has therefore been that the development of a large number of valuable drugs may have been terminated by risk-averse sponsors at an early stage due to perceived proarrhythmic risk.[20,29] De Ponti estimated that as many as 60 % of new molecular entities developed as potential therapeutic agents have been abandoned early in development for I_{Kr} blocking liability.[46] This is also supported by the trend of positive TQT studies, which has shown a decline from 60 % in 2005 to 10 % in 2012,[45] implying that many companies are probably abandoning a drug candidate with a pre-clinical signal of QT liability due to concerns that the drug would encounter significant challenges and regulatory hurdles at later stages of drug development. This raises legitimate questions on the impact of these guidelines on the promotion of public health, which, along with the protection of public health, is an equally important goal of regulatory authorities.[30]

Cost is an important factor that has influenced sponsors' approach to TQT studies. The need for conducting a TQT study for all drugs at the current cost of US$2-3 million, regardless of their pre-clinical effects on the I_{Kr} channel, is seen as a major financial burden, especially for pharmaceutical start-ups.[5,47] The likely therapeutic dose of the study drug is usually decided at the end of Phase II. The supra-therapeutic dose to be studied in a TQT study depends on plasma concentration levels seen in patients with hepatic or renal failure or with metabolic inhibitors.[32] As this information is usually available only by the end of Phase II, TQT studies for most drugs conducted to date have been conducted just prior to Phase III clinical development. The need to conduct the TQT study in late Phase II or early Phase III means that substantial costs are incurred even before the TQT

study is planned, and having to abandon a drug at this late stage could be financially challenging, justifying the adoption of a 'fail early, fail cheaply' strategy by many pharmaceutical companies.

The Early QT Assessment Strategy

To facilitate early internal decision making on the viability of continued development of drug candidates, many large pharmaceutical companies started collecting robust QTc data in early-phase single ascending dose (SAD) and multiple ascending dose (MAD) studies by incorporating the elements of rigorous ECG collection and analysis utilised in TQT studies.[5,48] These SAD and MAD studies often explore the highest concentrations ever tested in humans. While these studies are not statistically powered to detect a small QT change, robust ECG assessment in these studies can sufficiently improve the power to provide useful predictive information on clinically important QT liability, and hence inform critical go/no-go decisions or the timing of the TQT study.[49]

Additionally, characterisation of the concentration-QT relationship has become an important component of regulatory review of TQT studies since 2008.[50] This evaluation can be used in these early studies which, as just noted, often explore the highest concentrations ever tested for a drug candidate in humans, and also collect pharmacokinetic (PK) information that can be correlated with ECG data.[5] The collective experience over the last several years has shown that PK/QTc modelling making full use of paired PK and QTc data across a wide range of plasma concentrations improves the precision in estimating the QTc effect, and several published examples have shown concordance of Phase I PK/QTc modelling with TQT study results.[5]

FDA/CSRC Co-sponsored Think Tank, 2012

As a result of all these deliberations, in February 2012 the Cardiac Safety Research Consortium (CSRC)[51] held a Think Tank meeting at FDA Headquarters to discuss the various options for improving the confidence in QT assessment in early clinical development, and to assess circumstances under which such 'early QT assessment' could replace the TQT study.[5] This meeting discussed the FDA's perspective and industries' experience in using concentration-effect modelling for assessing a drug's effect on the QTc interval. The meeting also considered alternative approaches to demonstrate assay sensitivity in early clinical trials, such as autonomic maneouvres and food effects,[52,53] as well as quality criteria based on intra-subject variability and inter-baseline stability. These deliberations were aimed at potentially moving the definitive assessment of QTc prolongation from the end of Phase II into early in Phase 1 clinical development, thus allowing for informed decision-making at an early phase of the clinical drug development timeline. This would decrease resources expended on a separate TQT study by 'piggybacking' the QT assessment onto studies

routinely performed as part of clinical development.

To explore the validity of the early QT assessment strategy, a collaboration between the Consortium for Innovation and Quality in Pharmaceutical Development (IQ)[54] and the CSRC was formed in 2013. The IQ-CSRC group designed a clinical study in healthy participants to determine whether the TQT study could be replaced by robust ECG monitoring and exposure-response (ER) analysis of data generated from First-in-Human (FIH) SAD studies.[6] The 'IQ-CSRC Prospective Clinical Phase 1 Study' is a three-period, third-party blinded, randomised, placebo-controlled study in 20 healthy participants conducted in a design similar to a SAD Phase I study, with the primary objective being to estimate the effect of the drugs on the QTc interval using ER analysis. Six marketed drugs with well-characterised QT effects were selected for the evaluation, including five "QT-positive" drugs and one "QT-negative" drug. The QT-positive drugs were ondansetron, quinine, dolasetron, moxifloxacin, and dofetilide: the QT-negative drug was levocetrizine.

The QT-positive drugs were chosen after discussions with FDA. Selection criteria included a drug's toxicity profile (did it allow ethical administration of the drug to healthy participants?), lack of substantial heart rate effect, and the degree of QTc prolongation. The lower dose utilised on Day 1 was recommended by the FDA, and is meant to achieve a mean placebo-corrected, change-from-baseline QTc (ΔΔQTc) of 9 -12 msec. A higher dose, expected to result in ΔΔQTc of around 15-20 msec, was given on Day 2. The higher dose was chosen to mimic a typical SAD study. In addition to similarity with a SAD design, the higher dose was intended to increase the precision of the slope of the estimated ER model when data from the two dose levels were pooled. ECG recording, processing, and analysis were performed using rigorous methods as currently used in TQT studies.

It was agreed ahead of time that if the results of the study were to show a positive QT-prolonging effect (upper bound of QTc change from baseline ≥10ms at mean C_{max}) by concentration-effect modelling (CEM) for all five "QT-positive drugs," and additionally excluded a QTc effect for levocetirizine (the negative control drug), it would be deemed to have met its objective successfully.[5,6]

Results of the IQ-CSRC Study

Twenty healthy participants were randomised to a three-period crossover study design, where they received three of the six study drugs or placebo in an incomplete block design that resulted in each study drug being administered to nine subjects and placebo being administered to six subjects in separate periods.

Results showed that the upper bound of the 90% confidence interval (CI) of the mean predicted placebo-adjusted QTc change from baseline at geometric Cmax with all five QT-positive drugs exceeded 10 msec, and that the slope of the ER model was positive for all of these five drugs. In contrast, the upper bound for levocetrizine (the negative control drug) was less than 10 msec even when a single dose comprising six times the therapeutic dose was administered.

Using data from nine participants in each group treated with the study drug and six participants receiving placebo, the means (90% CI) of the predicted ΔΔ QTcF at geometric C_{max} were as follows: 9.5 msec (7.2, 13.5) for ondansetron; 9.8 msec (6.7, 17.3) for quinine; 6.8 msec (3.4, 11.6) for dolasetron; 11.7 msec (10.6, 17.9) for moxifloxacin; 11.3 msec (6.1, 14.6) for dofetilide; and 2.0 msec (-2.6, 6.0) for levocetrizine.

While two participants received placebo in a crossover design in this study, FIH studies usually do not involve a crossover placebo period. After excluding these two participants, results for seven participants who had received the study drug or placebo in a parallel design were similar.

While the study does serve as proof-of-concept, it has limitations and raises some concerns:[55]

1. Clinically relevant plasma concentrations of the drug and its metabolites are usually not known in early-phase clinical development. Doses tested may sometimes be lower than the eventual therapeutic doses.
2. Choice of ECG time points is limited by lack of knowledge of the pharmacokinetics of the parent drug and metabolites.
3. SAD studies may be too short to detect delayed effects. There is a need to demonstrate retrospectively that relevant concentrations and time points were studied.
4. The absence of a positive control to verify assay sensitivity in the proposed early-phase QT studies raises concerns about the risk of false negatives, i.e., the study excludes a QT effect for a drug that has one.
5. ER modelling is not standardised and the results can be operator- and model-dependent.
6. The utility of this approach using challenging compounds remains to be evaluated. This includes drugs with prominent effects on heart rate, drugs that affect QT by mechanisms other than hERG channel blockade, drugs with slow elimination, and drugs with poor tolerability.
7. Drugs with long half-lives of the parent drug or active metabolites may need to be studied in MAD studies. The IQ-CSRC study did not address the design or analysis required in MAD studies.

Implications of these Results for the Near- and Long-term Future of Cardiac Safety Assessment

There has been some discussion in recent publications on replacing the TQT by incorporating robust ECG monitoring during early Phase I studies.[56,57] The successful outcome of the IQ-CSRC study has already triggered discussions

on whether a similar approach could serve regulatory agencies, who may now accept this as an alternate path to replace the TQT study. It is believed that the ICH E14 Discussion Group activities for 2015 will include a review of the data from the IQ-CSRC study, as well as drug development programmes with ECG data from both SAD and MAD studies and thorough ECG studies.[55] The group is also expected to reflect upon the role of a positive control in ECG assessment. If these discussions lead to a change in regulatory position, this could be addressed by an updated "Question & Answers" document or revision to the ICH E14 Guideline itself.

Should this occur, however, it would not involve a considerable reduction in the amount of rigorous clinical QT assessment needed; it would simply transfer the intense ECG collection and analysis activity from TQT studies to early-phase studies. Methodological rigour would be equally as critical a component of QT evaluation in early-phase investigation as it has been for TQT studies. Based on the authors' recent experience, the average number of ECGs in a typical TQT study is approximately 10,000. A typical FIH SAD study has six to eight dose groups with eight participants in each group. The number of time points would be comparable to a TQT study (approximately 12 time points). In most TQT studies, triplicate ECGs are acquired at each of these time points. Based on these assumptions, the number of ECGs projected in a typical SAD study would be estimated to average around 2000-2500. Although these calculations are based on the assumption that triplicate ECGs are recorded at each time point, it should be recalled that 10 replicate ECGs were recorded at each time point in the IQ-CSRC early clinical phase QT study discussed in this paper. Several replicate ECGs are recorded at each time point to decrease the between- and within-subject variability in placebo-adjusted change from baseline in the QTc interval. A previous study has shown that increasing the replicate number of ECGs beyond four results in a progressive decline in benefit.[58] The ideal number of replicate ECGs that would be required in ECG-intensive SAD studies requires further research.

Typically, SAD/MAD studies outnumber TQT studies by far due to attrition at various stages of drug development related to safety or efficacy concerns. The clinical trials registry of the United States National Library of Medicine has 373 SAD/MAD studies registered in the three year period 2010-2012. In the corresponding period, 46 TQT studies were registered on the website. A review of the clinical pharmacology studies conducted by a large pharmaceutical company during a recent three-year period likewise showed a yearly average of three TQT studies and 24 SAD/MAD studies. Therefore, assuming that there will be eight times as many SAD/MAD studies as TQT studies, that conservatively 50 % of these will be ECG-intensive, and the number of ECGs in each such early-phase study will be 25 % of those in a TQT study (2500 ECGs vs. 10,000 ECGs), the number of ECGs for which sponsors will need to obtain central reading will essentially remain similar to the number required at current TQT study volumes. One option that some sponsors may choose in some cases is to collect high-quality ECG data in SAD/MAD studies, store the digital ECGs, but defer centralised analysis until later phases of development, by when it will be clear whether or not there are other safety issues and whether or not the preliminary efficacy data seem favourable.

For the initial years until consensus, experience, and confidence develop, and guidelines are amended and accepted in all major regulatory regions, it is possible that sponsors may be encouraged or choose to do both ECG-intensive early-phase studies and TQT studies. Thorough ECG studies may still be needed when the sponsor does not accept evidence of an ECG effect in SAD/MAD studies, regulators do not accept lack of evidence of an ECG effect in SAD/MAD studies, or when either/both parties believe that effects in SAD/MAD studies need further characterisation.

A limitation that the early-phase QT evaluation approach shares with the thorough ECG study is that it continues to rely on an imperfect surrogate for predicting proarrhythmic risk. It is hoped that in the longer term this would be addressed by the ongoing efforts to develop the Comprehensive *in vitro* Proarrhythmia Assay (CIPA), a new preclinical cardiac safety paradigm to directly assess proarrhythmic risk using a combination of non-clinical *in vitro* and *in silico* models.[59,60] This will be complementary to clinical ECG assessment, which will continue to be important.

This is an exciting time for the cardiac safety world. Though the past response to the issue of QT liability and drug-induced TdP has been over-engineered and resource-intensive, it has worked well, albeit with the unintended consequence of higher attrition of potentially valuable drugs. The proposed modifications of the cardiac proarrhythmia safety paradigm seek to build on this success while addressing some of the limitations of the current strategy of proarrhythmic risk assessment. This is likely to trigger a change from an environment in which a dedicated TQT study is conducted in later phases of clinical development to an intensive ECG evaluation in the early phase of drug development using existing FIH studies. ECG evaluation will thus continue to remain an important tool to assess proarrhythmic cardiac safety.

References

1. Turner JR, Durham TA. Integrated Cardiac Safety: Assessment Methodologies for Noncardiac Drugs in Discovery, Development, and Postmarketing Surveillance. Hoboken, NJ: John Wiley & Sons; 2009.
2. ICH S7B Guideline. The non-clinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human

pharmaceuticals. May 2005. Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S7B/Step4/S7B_Guideline.pdf (Accessed 23 November 2014).
3. ICH E14 Guideline. ICH E14 Guideline: the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. May 2005. Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E14/E14_Guideline.pdf (Accessed 23 November 2014).
4. E14 Implementation Working Group. ICH E14 Guideline: the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. Questions & Answers (R2). March 2014. Available at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E14/E14_QAs_R2_Step4.pdf (Accessed 23 November 2014).
5. Darpo B, Garnett C, Benson CT, et al. Cardiac Safety Research Consortium: can the thorough QT/QTc study be replaced by early QT assessment in routine clinical pharmacology studies? Scientific update and a research proposal for a path forward. Am Heart J. 2014;168:262-72.
6. Darpo B, Sarapa N, Garnett C, et al. The IQ-CSRC prospective clinical Phase 1 study: "Can early QT assessment using exposure response analysis replace the thorough QT study?" Ann Noninvasive Electrocardiol. 2014;19:70-81.
7. Strnadova C. The assessment of QT/QTc interval prolongation in clinical trials: A regulatory perspective. Drug Inf J. 2005;39:407–433.
8. Shah RR. Drugs, QT interval prolongation and ICH E14: the need to get it right. Drug Saf. 2005;28:115-25.
9. Food and Drug Administration, HHS. International Conference on Harmonisation; guidance on E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs; availability. Notice. Fed Regist. 2005;70:61134-5.
10. Shah RR. Drugs, QTc interval prolongation and final ICH E14 guideline: an important milestone with challenges ahead. Drug Saf. 2005;28(11):1009-28.
11. Darpo B, Nebout T, Sager PT. Clinical evaluation of QT/QTc prolongation and proarrhythmic potential for nonantiarrhythmic drugs: the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use E14 guideline. J Clin Pharmacol. 2006;46:498-507.
12. Hutmacher MM, Chapel S, Agin MA, Fleishaker JC, Lalonde RL. Performance characteristics for some typical QT study designs under the ICH E-14 guidance. J Clin Pharmacol. 2008;48:215-24.
13. Zhang J, Machado SG. Statistical issues including design and sample size calculation in thorough QT/QTc studies. J Biopharm Stat. 2008;18:451-67.
14. Zhang J. Testing for positive control activity in a thorough QTc study. J Biopharm Stat. 2008;18:517-28.
15. Turner JR. 2009, Interpreting the interval: design, conduct, analysis, and interpretation of the ICH E14 Thorough QT/QTc Study. European Pharmaceutical Contractor. 2009;September issue:64-66.
16. Turner JR. Japanese cardiac safety requirements: the rising of a new regulatory landscape. International Pharmaceutical Industry, 2010;Summer issue:64-67.
17. Darpo B. The Thorough QT/QTc Study 4 years after the implementation of the ICH E14 guidance. Br J Pharmacol. 2010;159:49-57.
18. Satin LZ, Durham TA, Turner JR. Assessing a drug's proarrhythmic liability: an overview of computer simulation modeling, nonclinical assays, and the Thorough QT/QTc Study. Drug Inf J. 2011:45;357-375.
19. Shah RR, Morganroth J. ICH E14 Q & A (R1) document: perspectives on the updated recommendations on thorough QT studies. Br J Clin Pharmacol. 2013;75:959-65.
20. Shah RR, Morganroth J, Kleiman RB. ICH E14 Q&A(R2) document: commentary on the further updated recommendations on thorough QT studies. Br J Clin Pharmacol. 2014 Jul 24. [Epub ahead of print]
21. Darpo B, Benson C, Dota C, et al. Results from the IQ-CSRC prospective study support replacement of the through QT study by QT assessment in the early clinical phase. Clin Pharmacol Ther. Accepted Article, doi: 10.1002/cpt.60.
22. Turner JR, Kothari S, Cabell CH, et al. Fifteen years of cardiac safety: history, state-of-the-science research, and glimpses into the future. International Pharmaceutical Industry. 2013;5(1):110-119.
23. Redfern WS, Bialecki R, Ewart L, et al. Impact and prevalence of safety pharmacology-related toxicities throughout the pharmaceutical life cycle. J Pharmacol Toxicol Methods. 2010; 62:e29.
24. Turner JR, Panicker GK, Karnad DR, Cabell CH, Lieberman R, Kothari S. Cardiovascular Safety Monitoring During Oncology Drug Development and Therapy. Am J Ther. 2014;21:512-22.
25. Valentin JP. Reducing QT liability and proarrhythmic risk in drug discovery and development. Br J Pharmacol. 2010; 159:5-11.
26. Hancox JC, McPate MJ, El Harchi A, Zhang YH. The hERG potassium channel and hERG screening for drug-induced torsades de pointes. Pharmacol Ther. 2008;119:118-32.
27. Salvi V, Karnad DR, Panicker GK, Kothari S. Update on the evaluation of a new drug for effects on cardiac repolarization in humans: issues in early drug development. Br J Pharmacol. 2010; 159:34-48.
28. Heijman J, Voigt N, Carlsson LG, Dobrev D. Cardiac safety assays. Curr Opin Pharmacol. 2014;15:16-21.
29. Kleiman RB, Shah RR, Morganroth J. Replacing the thorough QT study: reflections of a baby in the bath water. Br J Clin Pharmacol. 2014;78:195-201.
30. Stockbridge N, Morganroth J, Shah RR, Garnett C. Dealing with global safety issues: was the response to QT-liability of non-cardiac drugs well coordinated? Drug Saf. 2013;36:167-82.
31. Bouvy JC, Koopmanschap MA, Shah RR, Schellekens H. The cost-effectiveness of drug regulation: the example of thorough QT/QTc studies. Clin Pharmacol Ther. 2012;91:281-8.
32. European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products (CPMP). Points to consider: the assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products. CPMP/986/ 96. London, 17 Dec 1997. Available at: http://www.fda.gov/ohrms/dockets/ac/03/briefing/pubs/cpmp.pdf. (Accessed 23 November 2014).
33. Hingorani P, Karnad DR, Panicker GK, et al. Differences between QT and RR intervals in digital and digitized paper electrocardiograms: contribution of the printer, scanner, and digitization process. J Electrocardiol. 2008;41:370-5.
34. Panicker GK, Karnad DR, Natekar M, et al. Intra- and interreader variability in QT interval measurement by tangent and threshold methods in a central electrocardiogram laboratory. J Electrocardiol. 2009;42:348-52.
35. Panicker GK, Karnad DR, Joshi R, et al. Z-score for benchmarking reader competence in a central ECG laboratory. Ann Noninvasive Electrocardiol. 2009;14:19-25.
36. Salvi V, Karnad DR, Panicker GK, et al. Comparison of 5 methods of QT interval measurements on electrocardiograms from a thorough QT/QTc study: effect on assay sensitivity and categorical outliers. J Electrocardiol. 2011;44:96-104.
37. Salvi V, Karnad DR, Panicker GK, et al. Limb lead interchange in thorough QT/QTc studies. J Clin Pharmacol. 2011;51:1468-73.
38. Stockbridge N, Zhang J, Garnett C, Malik M. Practice and challenges of thorough QT studies. J Electrocardiol. 2012;45:582-7.

39. Salvi V, Karnad DR, Kerkar V, et al. Choice of an alternative lead for QT interval measurement in serial ECGs when Lead II is not suitable for analysis. Indian Heart J. 2012;64:535-40.
40. 40. Hingorani P, Karnad DR, Ramasamy A, et al. Semiautomated QT interval measurement in electrocardiograms from a thorough QT study: comparison of the grouped and ungrouped superimposed median beat methods. J Electrocardiol. 2012;45:225-30.
41. Salvi V, Karnad DR, Kerkar V, et al. Comparison of two methods of estimating reader variability in QT interval measurements in thorough QT/QTc studies. Ann Noninvasive Electrocardiol. 2014;19:182-9.
42. Natekar M, Karnad DR, Salvi V, et al. Reader variability in QT measurement due to measurement error and variability in leads selection: a simulation study comparing 2-way vs. 3-way interaction ANOVA model. J Electrocardiol. 2014;47:140-3.
43. Johannesen L, Garnett C, Malik M. Electrocardiographic data quality in thorough QT/QTc studies. Drug Saf. 2014;37:191-7.
44. Johannesen L, Garnett C, Malik M. Impact of electrocardiographic data quality on moxifloxacin response in thorough QT/QTc studies. Drug Saf. 2014;37:183-9.
45. Park E, Willard J, Bi D, Fiszman M, Kozeli D, Koerner J. The impact of drug-related QT prolongation on FDA regulatory decisions. Int J Cardiol. 2013;168:4975-6.
46. De Ponti F. Pharmaceutical and regulatory aspects of QT prolongation. In Vas RJ, Klabunde T (Eds), Antitargets: Prediction and Prevention of Drug Side Effects. Weinheim, Germany: Wiley-VCH.
47. Chi KR. Revolution dawning in cardiotoxicity testing. Nat Rev Drug Discov. 2013;12:565-7.
48. He YL, Zhang Y, Yan JH, et al. High-quality triplicate electrocardiogram monitoring in a first-in-man study: potential for early detection of drug-induced QT prolongation. Int J Clin Pharmacol Ther. 2013;51:948-57.
49. Sethuraman V, Sun Q. Impact of baseline ECG collection on the planning, analysis and interpretation of 'thorough' QT trials. Pharm Stat. 2009;8:113-24.
50. Garnett CE, Beasley N, Bhattaram VA, et al. Concentration-QT relationships play a key role in the evaluation of proarrhythmic risk during regulatory review. J Clin Pharmacol. 2008; 48: 13-8.
51. CSRC web site. Available at: http://www.cardiac-safety.org/ (Accessed 23 November 2014).
52. Taubel J, Wong AH, Naseem A, Ferber G, Camm AJ. Shortening of the QT interval after food can be used to demonstrate assay sensitivity in thorough QT studies. J Clin Pharmacol. 2012;52:1558-65.
53. Hnatkova K, Kowalski D, Keirns JJ, van Gelderen EM, Malik M. QTc changes after meal intake: sex differences and correlates. J Electrocardiol. 2014 Aug 2. [Epub ahead of print]
54. International Consortium for Innovation & Quality in Pharmaceutical Development. Available at: https://iqconsortium.org/ (Accessed 23 November 2014).
55. Strnadova C. Is there sufficient scientific support for replacing the E14 Guidance with a new paradigm? Talk given at the 1st DIA China Drug-induced Cardiovascular Toxicity Workshop, Beijing, China, November 23-24, 2014.
56. Sager PT, Kowey P. The thorough QT study: Is its demise on the horizon? Ann Noninvasive Electrocardiol. 2014;19:1-3.
57. Salvi V, Karnad D, Kothari S, et al. The contribution of early-phase clinical data to a drug's integrated cardiac safety portfolio. Journal for Clinical Studies. 2011;3:26-31
58. Natekar M, Hingorani P, Gupta P, et al. Effect of number of replicate electrocardiograms recorded at each time point in a thorough QT study on sample size and study cost. J Clin Pharmacol. 2011;51:908-14.
59. Sager PT, Gintant G, Turner JR, Pettit S, Stockbridge N. Rechanneling the cardiac proarrhythmia safety paradigm: a meeting report from the Cardiac Safety Research Consortium. Am Heart J. 2014; 167:292-300.
60. Cavero I, Holzgrefe H. Comprehensive in vitro Proarrhythmia Assay, a novel in vitro/in silico paradigm to detect ventricular proarrhythmic liability: a visionary 21st century initiative. Expert Opin Drug Saf. 2014;13:745-58.

Snehal Kothari, MD, DM, FACC, FESC, is a Cardiologist and Senior Medical Director & Head of the Cardiac Safety Center of Excellence at Quintiles. He is widely published in the areas of electrocardiography and cardiac safety, and has supervised centralised ECG services for several hundred studies spanning all phases of drug development including thorough ECG studies.
Email: snehal.kothari@quintiles.com

Dilip R. Karnad, MD, FACP, FRCP (Glasg), is Head of the Quintiles Cardiac Safety Services Research Team. Until recently, he was Professor of Medicine at the Seth G S Medical College, Mumbai, India, and Adjunct Professor of Medicine, Baylor College of Medicine, Houston, TX, USA.
Email: dilip.karnad@quintiles.com

Gopi Krishna Panicker, BHMS, PGDCR, is Medical Writing Manager at Quintiles Cardiac Safety Services Research Team. He has authored/co-authored 24 peer-reviewed papers on ECG measurement methodology and variability, automated ECG algorithms and benchmarking of central lab processes.
Email: gopi.panicker@quintiles.com

J. Rick Turner, PhD, is a member of Quintiles' Cardiac Safety and Cardiovascular Centers of Excellence, and a member of the Cardiac Safety Research Consortium's Executive Committee. He has published more than 100 peer-reviewed papers and a total of 14 authored and edited books.
Email: rick.turner@quintiles.com