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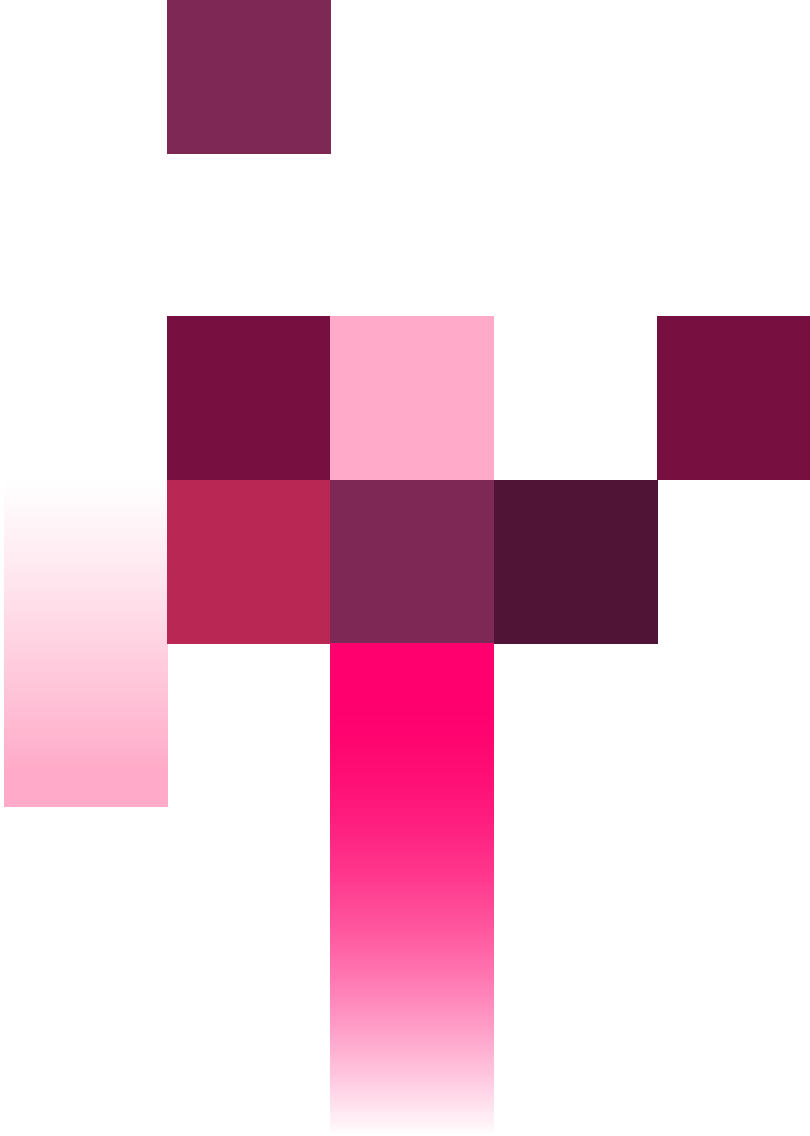

Benefits of centralized ECG reading in clinical oncology studies

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Benefits of Centralized ECG Reading in Clinical Oncology Studies

Robert Kleiman, MD[1], Jeffrey Litwin, MD[1], and Joel Morganroth, MD[1]

Abstract

Background: Many clinical trials of investigational oncologic agents utilize electrocardiogram (ECG) machine measurements of QTc, for inclusion/exclusion and dosing decisions, though their reliability in this setting has not been established. *Methods:* We compared the digital ECG machine QTc measurements with those obtained by a centralized ECG core lab on more than 270,000 consecutive ECGs collected from 299 clinical oncology trials. *Results:* The mean difference between the ECG machine measurements and the central measured QTcF was 1.8 $\pm$ 15.7 milliseconds. In addition, 29.7% of ECGs with an ECG machine–measured QTcF >450 milliseconds had a centrally measured QTcF <450 milliseconds, 44.6% of ECGs with an ECG machine–measured QTcF >470 milliseconds had a centrally measured QTcF <470 milliseconds, and 77.2% of ECGs with an ECG machine–measured QTcF >500 milliseconds had a centrally measured QTcF <500 milliseconds. The likelihood of a large discrepancy between the ECG machine– and centrally measured value for QTcF increased at both the high and low ends of the range of ECG machine QTcF measurements. *Conclusions:* While on average ECG machine–measured QTcF values were very similar to the central core lab measurements; there were very significant discrepancies which will have important implications for patient recruitment for clinical oncology trials as well as for patient safety during dosing with new oncologic agents. Reliance on ECG machine QTc measurements during clinical oncology trials may lead to unnecessary exclusion of patients as well as unneeded treatment interruptions.

Keywords

electrocardiography, clinical oncology trials, QTc, ECG machine

Introduction

The development of a new drug requires the demonstration of both clinical efficacy and safety. Hepatotoxicity and cardiac toxicity (particularly ventricular proarrhythmia and left ventricular dysfunction) are among the most common safety issues that lead to termination of a drug's development.[1] Since the 1970s, approximately a dozen approved drugs have been withdrawn from the market because of an excess of sudden cardiac deaths, now known to be due to drug-induced torsade de pointes (TdP).[2] Drugs that produce TdP have diverse chemical structures, but share the common characteristic of prolonging the QTc interval measured on the surface electrocardiogram (ECG).[3] The adoption of the International Conference for Harmonization (ICH) E14 Guidance for Industry in 2005 has made the evaluation of a new drug's effect on the QTc interval mandatory.[4] Since many oncologic agents are cytotoxic and/or genotoxic and cannot be safely dosed in healthy individuals, the QTc assessment of such drugs must be performed in clinical trials involving oncology patients. Many oncologic agents prolong the QTc interval, and it is therefore necessary in most clinical trials to set inclusion/exclusion criteria based on the QTc interval and to set QTc criteria for holding or terminating therapy during the conduct of the trial.[5] Oncologic agents that are known to prolong the QTc interval include arsenic trioxide,[6] sunitinib,[7] nilotinib,[8] and vandetanib.[9]

Clinical sites participating in oncology trials may record ECGs on their own (site) ECG machines or may utilize devices supplied by a centralized ECG core laboratory. The majority of ECGs in clinical oncology trials currently are not centralized, and ECG cardiac safety is determined based solely on the site's own ECG assessment. Most oncologists are not expert electrocardiographers, and few oncology sites have ECGs evaluated

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by a cardiologist (though even most cardiologists are not particularly skilled at QTc measurement).[10] In the absence of the high-precision ECG measurements performed by an ECG core laboratory, most clinical sites therefore rely on automated ECG machine algorithms for the measurement of the ECG intervals, including QT, heart rate (HR), and the HR-corrected QT (QTc). QTcF (the Fridericia correction) is increasingly preferred during clinical oncology trials because of the shortcomings of QTcB (the Bazett QT correction), which tends to overcorrect at HR >75-80 bpm, although QTcB is still used in some trials. Common inclusion criteria in oncology trials are QTc <450 or <470, and a common threshold for holding or terminating treatment in oncology trials is a QTc >500 milliseconds. There is a general perception that ECG machine measurements of QTc are accurate and precise, but it is less widely known that ECG machine algorithms may significantly undermeasure or overmeasure the QT interval and the HR, leading to errors in the derived value of QTc.[11] We, therefore, retrospectively analyzed the results of a large series of consecutive ECGs collected during a series of clinical oncology trials to evaluate the reliability of ECG machine measurements of QTc when compared with the measurements obtained at a centralized ECG core laboratory.

Methods

From a set of 1,000,000 consecutive ECGs collected during a wide range of clinical drug development trials utilizing eResearch Technology (ERT) as a centralized core lab, we selected all ECGs collected during clinical oncology trials. All ECGs were collected digitally on ECG machines validated and provided to the sites by ERT. ECGs were collected on ECG machines manufactured by Mortara Instruments, which utilized the VERITAS algorithm to generate ECG machine measurements, or by GE Healthcare, which utilized the 12-SL algorithm.[12,13] ECGs were transmitted digitally to ERT or were recorded on continuous digital 12-lead Holters and were stored on digital flashcards, from which ERT extracted 12-lead ECGs that were processed using the Mortara VERITAS algorithm prior to measurement by ERT personnel. The ECG machine algorithm measurements were stored in the ERT database but were deleted from the digital ECG file prior to measurement by ERT personnel, except for protocols that used a superimposed global median beat measurement methodology, in which case the ECG machine measurements were adjudicated directly by ERT personnel.

ERT measurements were performed in the ERT EXPERT system (eResearch Technology Inc, Philadelphia, PA) using a semiautomated process combining an algorithm for initial caliper placement followed by review of all ECGs by a minimum of 1 highly trained technician and 1 cardiologist. Measurements were performed on 3 consecutive beats on a single lead (usually lead II). ECG algorithm caliper placements judged to be incorrect were adjusted by the ERT technicians. ECGs for protocols specifically designed to evaluate the QT effects of a drug had a single reader (technician) for each subject. The number of readers (technicians) was selected based on the size and duration of the trial. One to 5 cardiologists were involved in the review of the ECGs from each protocol, again depending on the size and duration of the trial. ECGs with out-of-range measurements or poor technical quality were also reviewed by a second set of quality control technicians. All ECG measurements were then reviewed by a cardiologist, who could also revise measurements as necessary. Approximately 20% of ECGs were measured using a superimposed global median beat methodology in which a single set of caliper placements performed on one superimposed beat from each lead was reviewed by the technician. (Nearly all ECG machine algorithms, including the GE 12SL and Mortara VERITAS algorithms, use a global median beat methodology, with proprietary weighting of the various leads.) With either measurement methodology, approximately 60% of ECGs required manual adjustment by ERT technicians of one or more caliper positions.

As an additional step to insure correct ECG measurements, all ECGs with measurements outside the normal range, all ECGs with quality assessed to be less than ideal, and 5% of all other ECGs selected at random went through an additional review (and if necessary, adjudication) by a second set of trained technicians. Finally, all ECGs were reviewed by a cardiologist, who also had the opportunity to revise measurements (only 1%-2% of ECGs required additional manipulation of the calipers by the reviewing cardiologist).

The patient randomization status (pre- or post-randomization) was available for most ECGs, but the details of the trial design and the randomization codes were not known to ERT, and for purposes of patient confidentiality, none of the clinical characteristics of the patients were known. Thus, the prior cardiac history and concomitant medications were not available.

Results

A total of 270,144 consecutive ECGs that had both the ECG machine and ERT measurements available for comparison were collected from 18,199 individual patients during 299 clinical oncology trials; 22,171 ECGs were recorded at screening, 20,109 ECGs were recorded at baseline or at the time of randomization (but prior to first dose of the experimental regimen), 215,715 were recorded during treatment, 1819 ECGs were recorded at trial termination or during follow-up, and for 13,050 ECGs the randomization status was unknown. The age, gender, prior medical history, oncologic indication, and concurrent medications were not known for any patients. There were 217,977 ECGs measured using 3 beats in a single lead,

Table 1. Effect of measurement methodology and randomization status on QTc.

	Number of ECGs	Mean ECG Machine QTcF (ms)	Mean Centralized QTcF (ms)	Mean Difference Between ECG Machine and Centralized QTcF (ms, ± SD)	Mean ECG Machine QTcB (ms)	Mean Centralized QTcB (ms)	Mean Difference Between ECG Machine and Centralized QTcB (ms, ± SD)
Superimposed global median beat	52,167	425.4	426.9	1.5 ± 11.5	425.4	426.9	1.5 ± 12.0
3 beats in a single lead	217,977	413.7	415.5	1.8 ± 16.6	429.1	430.8	1.7 ± 17.8
Prerandomization	41,380	409.9	411.2	1.3 ± 14.5	424.5	425.7	1.2 ± 15.6
Postrandomization	215,714	414.5	416.4	1.9 ± 15.7	429.0	430.7	1.8 ± 16.8
Randomization status unknown	13,050	417.3	418.7	1.4 ± 18.9	432.2	433.3	1.1 ± 20.6
All ECGs	270,144	414.0	415.7	1.8 ± 15.7	428.4	430.1	1.7 ± 16.8

and 52,167 measured using a superimposed global median beat methodology.

For QTcB, the mean difference between the ECG machine and the ERT measurement was 0.03 ± 32.2 milliseconds, and for QTcF, the mean difference between the ECG machine and the ERT measurement was 1.8 ± 15.7 milliseconds (Table 1). The differences between the ECG machine and centralized measurements of QTcF are shown in Table 2. In this study, 3.6% of the ECGs had a difference between the ECG machine and centralized measurements ≥30 milliseconds, and for 1.2%, the difference was >60 milliseconds. When there were large discrepancies between the 2 QTcF measurements, the ECG machine–measured QTcF was usually greater than the centralized measurement.

Table 2. Magnitude of difference between ECG machine and centralized QTcF measurements.

Difference Between ECG Machine and Centralized QTcF (ms)	Number of ECGs (% of Total ECGs)	Machine QTcF > Centralized QTcF (% of Category)	Centralized QTcF > Machine QTcF (% of Category)
>60	3131 (1.2)	2401 (77)	730 (23)
30-60	6616 (2.4)	4239 (64)	2377 (36)
20-29	14,572 (5.4)	8842 (61)	5730 (39)
10-19	60,263 (22.3)	35,032 (58)	25,231 (42)
1-9	136,429 (50.5)	73,646 (54)	62,783 (48)
0	49,133 (18.2)	—	—

We specifically looked at the common inclusion criteria of QTcF <450 or <470, and the common threshold for holding or terminating treatment of QTcF >500 milliseconds. The results are shown in Table 3. Of the 16,721 ECGs for which the ECG machine–measured QTcF was ≥450 milliseconds, the centrally measured QTcF was <450 milliseconds for 29.7%. Of the 4208 ECGs for which the ECG machine–measured QTcF was ≥470 milliseconds, the centrally measured QTcF was <470 milliseconds for 44.6%. Of the 812 ECGs for which the ECG machine–measured QTcF was ≥500 milliseconds, the centrally measured QTcF was <500 milliseconds for 77.2%. An example of an ECG with an incorrect ECG machine–measured QTcF is shown in Figure 1. The ECG machine incorrectly measured the QT interval as 512 milliseconds, while the centrally measured QT interval was 299 milliseconds. This resulted in an ECG machine QTcF value of 644 milliseconds, while the centralized QTcF was 376 milliseconds.

An evaluation of ECGs for which the ECG machine QTcF measurements was relatively low also demonstrated wide differences between the ECG machine algorithm and centralized QTcF measurements (Table 4). There were 6665 ECGs with ECG machine QTcF measurements ≤370 milliseconds; the mean difference between the ECG machine– and the centrally measured QTcF was 36.3 ± 45.3 milliseconds, and nearly 4% of these ECGs had a centrally measured QTcF >450 milliseconds. There were 530 ECGs with ECG machine QTcF measurements ≤320 milliseconds; the mean difference between the ECG machine– and the centrally measured QTcF was 125 ± 51.8 milliseconds, and nearly 10% of these ECGs had a centrally measured QTcF >450 milliseconds. At both ends of the range of QTc measurements, the higher or lower the ECG machine–measured value of QTcF, the higher the likelihood of a significant difference between the ECG machine measurement and the centralized measurement.

The centralized ECG measurements used 2 different measurement methodologies: measurements performed on 3 consecutive beats from a single lead or on a superimposed global median beat. For both QTcF and QTcB, the difference between the ECG machine and the centralized core lab measurements were similar, with both centralized measurement methodologies. The standard deviation of the difference between the ECG machine and the centralized measurements was greater for measurements of 3 beats in a single lead than for the global median beat methodology (SD = 17.8 vs 12.0 milliseconds).

Table 3. Comparison of ECG machine and centralized measurements of QTcF: Long range of machine-measured QTc.

ECG Machine QTcF (ms)	Number of ECGs	Mean ECG Machine QTcF (ms)	Mean Centralized QTcF (ms)	Mean Difference Between ECG Machine and Centralized QTcF (ms, ± SD)	Centralized QTcF below threshold value, n (%)
≥450	16721	465.0	456.8	–9.18 ± 26.65	4970 (29.7)
≥470	4208	488.3	464.5	–23.82 ± 44.35	1877 (44.6)
≥500	812	525.1	444.7	–80.48 ± 65.83	500 (77.2)

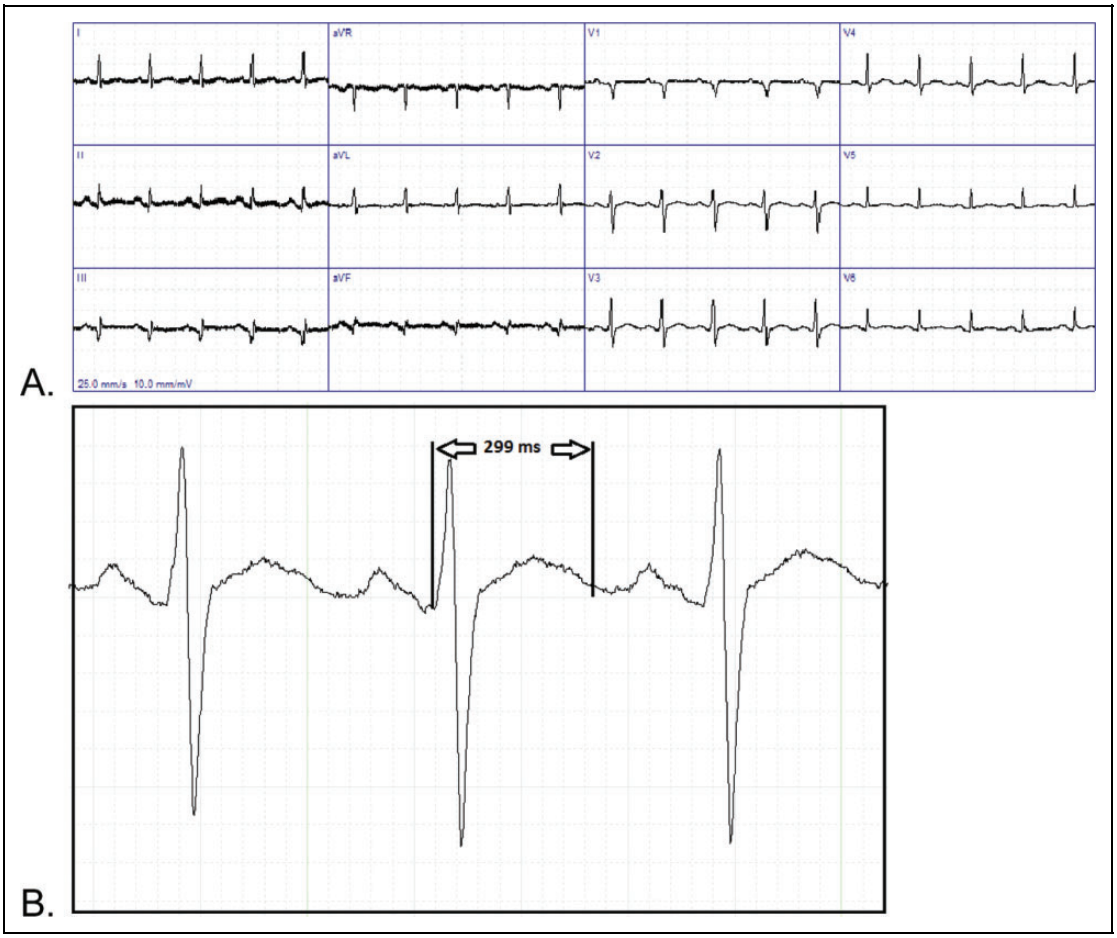

Figure 1. Electrocardiogram (ECG) machine–measured QT 512 milliseconds; QTcF 644 milliseconds; centrally measured QT 299 milliseconds; QTcF 376 milliseconds. (A) Full 12-lead ECG. (B) Magnification of lead V5.

Table 4. Comparison of ECG machine and centralized measurements of QTcF: Short range of machine-measured QTc.

ECG Machine QTcF (ms)	Number of ECGs	Mean ECG Machine QTcF (ms)	Mean Centralized QTcF (ms)	Mean Difference Between ECG Machine and Centralized QTcF (ms, ± SD)	Centralized QTcF >450 ms, n (%)
≤370	6665	352.4	388.7	36.3 ± 45.3	247 (3.7)
≤350	1883	324.0	407.2	83.2 ± 48.1	116 (6.2)
≤320	530	287.2	412.3	125 ± 51.8	52 (9.8)

In order to determine whether the difference between ECG machine QTc measurements and centralized core lab measurements might be magnified or reduced by study medications, an analysis was performed separately for ECGs recorded prior to or post randomization. Post-randomization ECGs tended to have higher QTc values, though the difference between the

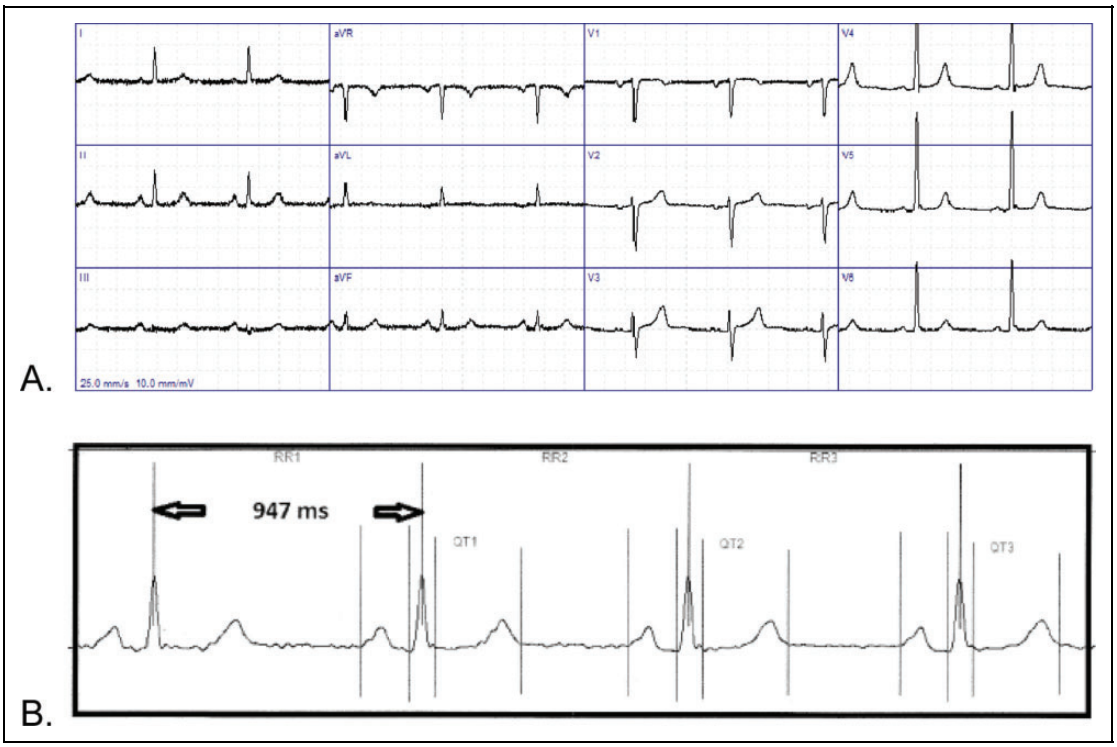

Figure 2. Electrocardiogram (ECG) machine measurements incorrect due to incorrectly measured heart rate and QT. ECG machine–measured HR 106 bpm; QT 210 milliseconds; QTcF 253 milliseconds. Centrally measured HR 63 bpm; QT 395 milliseconds; QTcF 402 milliseconds. (A) 12-lead ECG. (B) Magnification of lead II.

ECG machine and the centralized core lab QTc measurements did not differ greatly between pre- and post-randomization ECGs (Table 1).

The corrected QT interval, or QTc, is derived from the measurement of both the QT interval and the heart rate. An error by the ECG machine algorithm in either the QT or HR measurement will result in an incorrect calculated QTc value. An example is shown in Figure 2, demonstrating an ECG with significant high-frequency artifact, which the ECG machine misinterpreted as additional QRS complexes, resulting in a falsely elevated measured HR and thus a falsely elevated QTcF value.

Discussion

This study evaluated the difference between ECG machine and centralized core lab measurements of QTc for 270,144 consecutive ECGs collected during oncology clinical trials. The evaluation of a new drug's effect on the QTc interval is an important part of the development program for any new compound and is particularly important in oncology because of the large number of oncologic agents that are known to prolong the QTc interval. While the majority of clinical trials of new oncologic agents do involve the collection of ECGs, many clinical trials in oncology do not centralize measurement of their ECGs and rely upon site evaluation of the QTc and ECG interpretation. This study was therefore performed to compare ECG machine measurements (commonly used by a site when a central lab is not utilized) versus centrally generated ECG cardiac safety data.

Our findings demonstrate that the central tendency QTc measurements generated by ECG machine algorithms and by centralized core lab evaluation are quite similar, but large discrepancies between the ECG machine and centralized measurements are relatively common. Among the more than 270,000 ECGs evaluated in this study, the mean difference between the ECG machine and centralized measured QTcF was only 1.8 milliseconds, but with a standard deviation of 15.7 milliseconds. In particular, there were very wide variations between the ECG machine measurements and the centralized measurements (>20 milliseconds discrepancy) for 10% of ECGs; in most cases of large differences, the ECG machine QTcF measurement was greater than the centralized measurement. It also appears that the ECG machine measurements are more likely to be significantly different than the centralized measurements both when the ECG machine reports a prolonged or a very short value for QTcF.

Drugs can alter factors such as heart rate, T wave amplitude, and T wave morphology, which may affect the precision of ECG machine algorithm measurements. In order to evaluate

whether the difference between ECG machine and centralized QTc measurements might be magnified or reduced by treatment with study medications, we compared the differences between ECGs recorded prior to or following randomization. QTc was increased post randomization, though the difference between the ECG machine and centralized QTc measurements was unaffected. As we were blinded to the treatment allocations during these trials, it was not possible to directly examine the effect of specific drugs on ECG machine measurement precision.

Our findings have several implications for both investigators and sponsors of clinical trials in oncology. First, these results suggest that many patients who are excluded from participation in clinical trials due to an elevated ECG machine–measured QTc may actually have been eligible for study participation. Common exclusion thresholds for clinical trials are QTcF >450 milliseconds or QTcF >470 milliseconds. Our findings show that nearly 30% of the ECGs with an ECG machine–measured QTcF >450 milliseconds had a centrally measured QTcF <450 milliseconds, and nearly 45% of ECGs with an ECG machine–measured QTcF >470 milliseconds had a centrally measured QTcF <470 milliseconds. These ECG machine discrepancies may lead to the unnecessary exclusion of potential patients, prolonging the duration and cost of the trial, and denying access to potentially lifesaving investigational therapy to patients who have often exhausted all conventional therapies for their malignancies.

Our findings also have implications concerning the dosing decisions which are made during a clinical trial. It is common to set QTc thresholds in a clinical trial that determine whether a patient can receive a scheduled dose of the investigational product or even whether they can continue in the trial. A common threshold value is QTcF >500 milliseconds, as the risk of developing TdP increases significantly when the QTc increases surpasses this value. Our data demonstrated that 77% of ECGs that had an ECG machine–measured QTcF >500 milliseconds actually had a centrally measured QTcF <500 milliseconds. The use of ECG machine QTcF measurements during a trial thus has a significant risk of leading to unnecessary withholding of therapy or even of unnecessary withdrawal of a patient from the trial.

The present study evaluated the ECG machine measurements performed using 2 widely used ECG measurement algorithms, though in each of the clinical trials evaluated, only a single algorithm was used. In contrast, when ECGs are collected in a decentralized manner, the clinical sites generally use site-owned ECG machines, or may send their patients to another facility to have an ECG performed. Under such conditions, it is highly unlikely that all of the sites would use the same model of ECG machine or even the same ECG machine algorithm. This would likely result in even greater variability.

Another concern regards ECG machine measurements that are on the shorter end of the normal range. It is commonly assumed that if an ECG machine–measured QTcF is on the short side, then a patient's "true" QTcF must certainly be within normal limits. However, we found that for ECGs with machine–measured QTcF <370 milliseconds, the central measurement differed by 36.3 $\pm$ 45.3 milliseconds, and 3.7% of ECGs actually had a centrally measured QTcF >450 milliseconds. The lower the ECG machine measurement of QTcF, the greater the discrepancy between the ECG machine and centralized measurements. For ECGs with a machine–measured QTcF <320 milliseconds, the centrally measured QTcF differed by 125 $\pm$ 51.8 milliseconds, and 9.8% of ECGs had a centrally measured QTcF >450 milliseconds. Thus, both high and low ECG machine measurements of QTcF may lead to inclusion/exclusion errors and errors in administering or withholding dosages of an experimental therapy. This highlights the risk of selecting only ECGs with long ECG machine QTc measurements for centralized evaluation, as such a strategy would overlook many ECGs with "short-normal" ECG machine QTc measurements which have large measurement errors.

Limitations

There are several limitations to this study. This investigation was performed retrospectively, and only included ECGs from trials that utilized central core lab measurement of ECGs. These trials could have selected for drugs or patients for whom the ECG machine measurements were particularly challenging. However, there appeared to be little difference between our findings in pre- and post-randomization ECGs, suggesting that the investigational agents tested in these trials did not add to the differences between the machine and central core lab ECG measurements. We also evaluated all consecutive ECGs collected over a long time interval, including many different trials with differing designs, patient populations, and therapies with the aim of avoiding any selection bias. Nevertheless, it remains possible that the trials involved in this study were chosen for centralized ECG processing because they recruited patients with more complex cardiac disease and ECGs and, thus, might not be representative of the average oncology patient. In addition, since we were blinded to the patient demographics, we were unable to stratify the findings based on factors that may affect ECG findings, such as age, gender, or prior history. We also evaluated measurements from ECG machines from only 2 manufacturers, though these are the 2 largest manufacturers of the ECG devices used in clinical trials. We believe that the central core lab measurements were more accurate than the ECG machine measurements since all centralized measurements were confirmed by at least 2 and often 3 different individuals who were blinded to the details of patient

demographics as well as the trial design. Furthermore, central core lab ECG measurement is considered the gold standard for data to be included in a submission to regulatory authorities during the drug development process.

Conclusions

In conclusion, this study demonstrated that there were large differences between the QTc measurements generated by ECG machine algorithms and QTc measurements performed by a centralized core lab in a large number of consecutive ECGs collected during clinical oncology trials. The differences between the ECG machine and centralized core lab measurements were larger for QTcB than for QTcF and were highest for both very low and very high ECG machine QTc values. The use of ECG machine QTc measurements for screening purposes in clinical oncology trials may impeded recruitment of patients by leading to the unnecessary exclusion of patients with a false positive QTc elevation, and may also result in improper withholding of medication dosing. Investigators and sponsors of clinical oncology trials should consider the limitations of ECG machine measurements in planning the ECG collection strategies for their clinical trials.

Declaration of Conflicting Interests

The authors are employees of eResearch Technology Inc (ERT), a company that offers centralized ECG reading services to the biopharmaceutical industry. The authors have no other relevant conflicts of interest to disclose.

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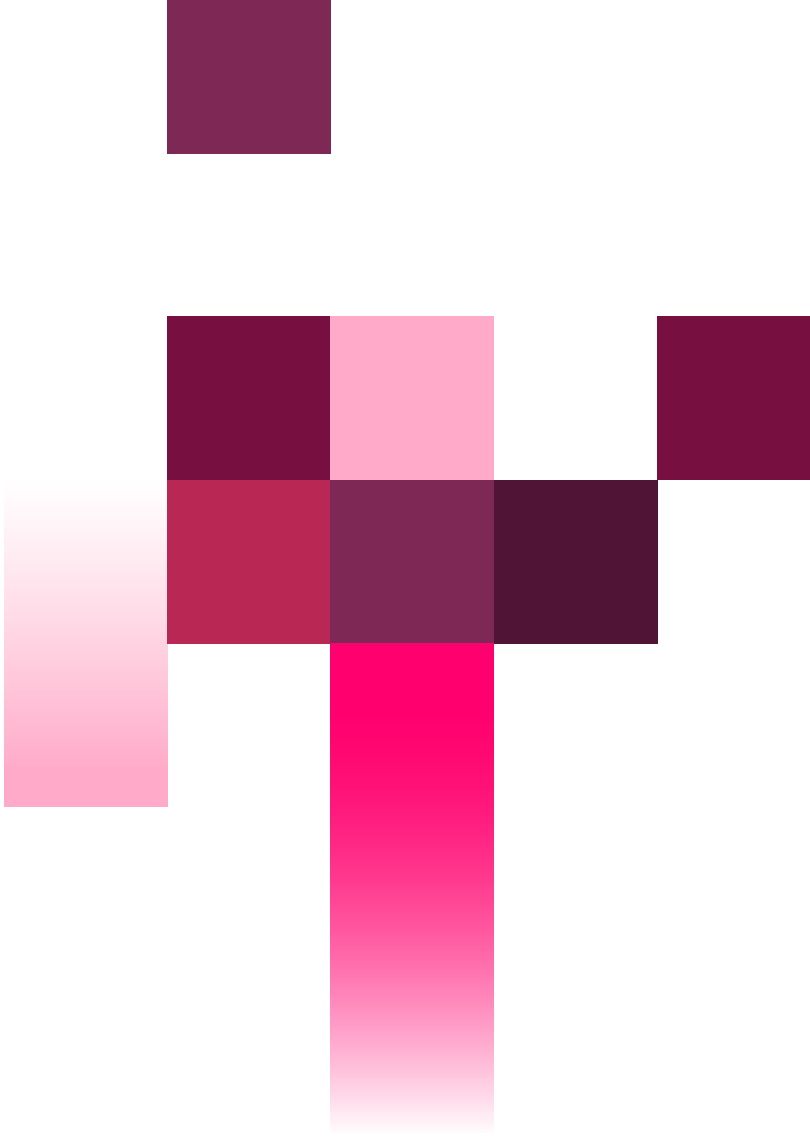

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