ECG Core Laboratory Approach to Drug testing

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Overview

- Introduction
  - Why should we test drugs for cardiac safety
  - Regulatory initiatives and the E14 document
- Core Lab Methods
  - Digital acquisition, blinding, analysis and archiving
- "Thorough QT" designs
- Quality Control
  - Best practices
  - Z scores
  - The Metrics Consortium and the FDA Warehouse
- Future Directions

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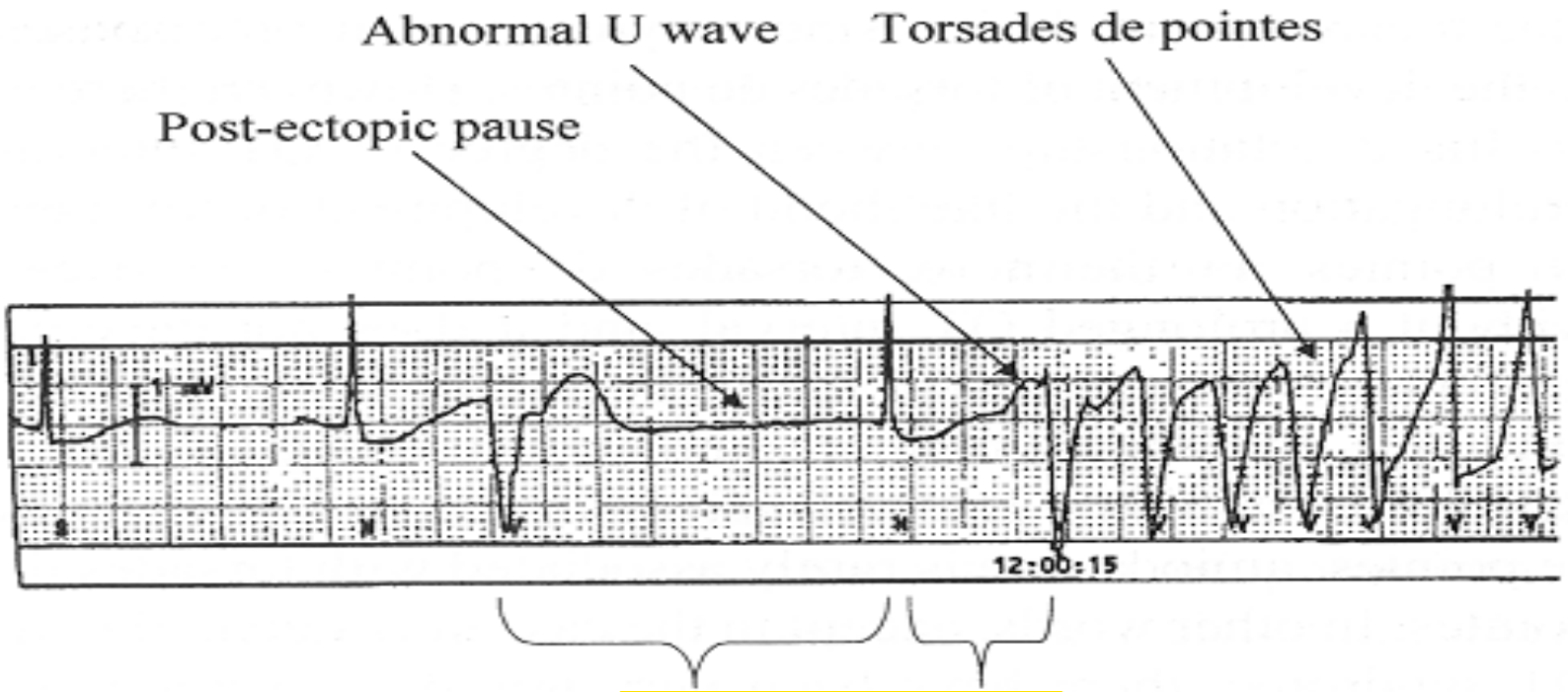
Why Record ECG's in Clinical Trials?



Scope of the Problem: Drugs with a Risk of Torsades de Pointes

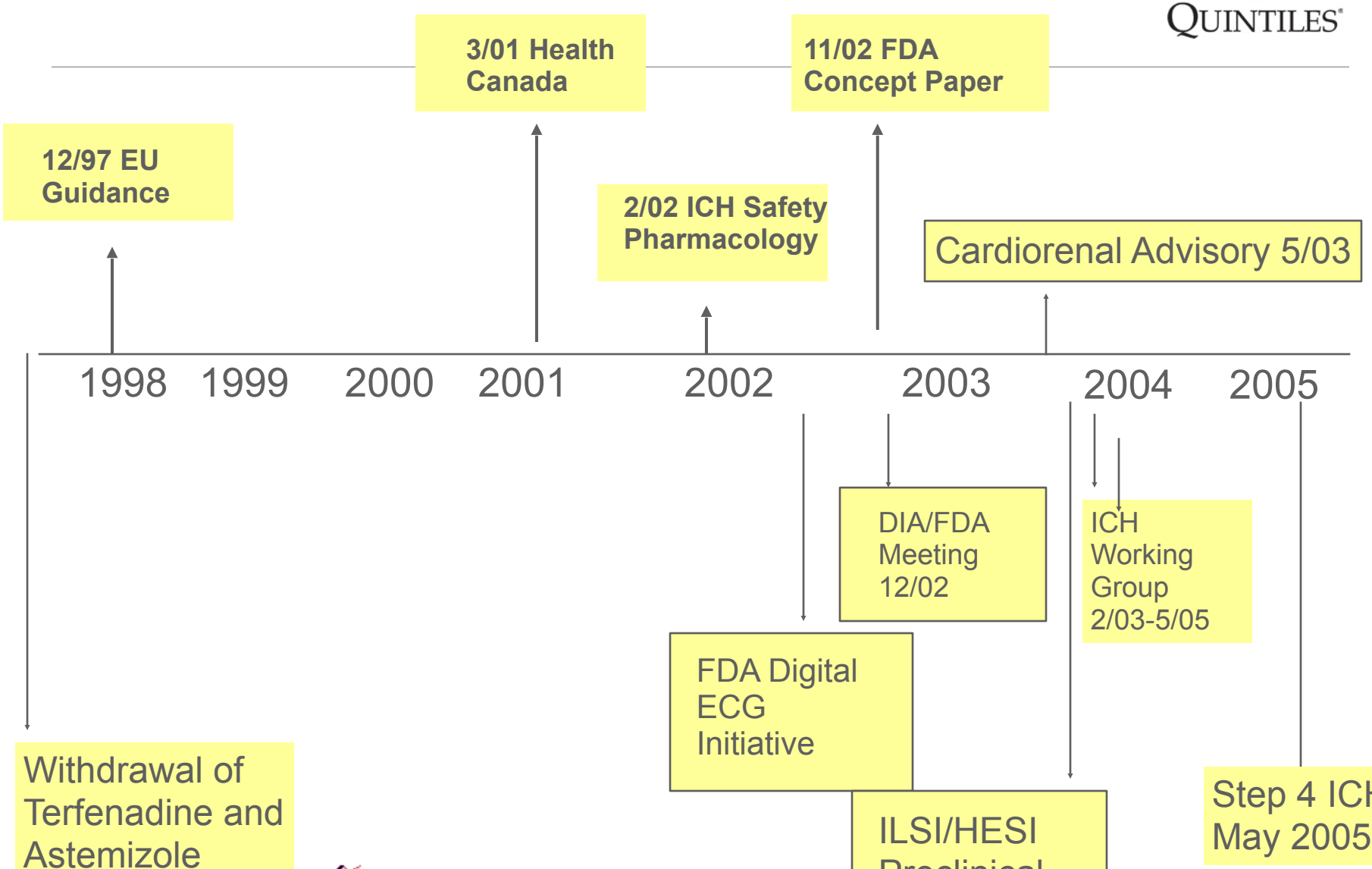
erythromycin	clarithromycin	dirithromycin	azithromycin
itraconazole	fluconazole	ketoconazole	sparfloxacin
grepafloxacin	ganciclovir	foscarnet	saquinavir
amiodarone	flecainide	sotalol	quinidine
procainamide	disopyramide	ibutilide	moricizine
Astemizole	cisapride	omeprazole	risperidone
Haloperidol	pimozide	mesoridazine	quietiapine
fluoxetine	desipramine	protriptyline	venlafaxine
nefazodone	bepridil	isradipine	nicardipine
penbutolol	salmeterol	albuterol	dolasetron
citalopram	tamoxifen	tolterodine	zolmitriptan
fluvoxamine	moexipril	LAAM	felbamate
fosphenytoin	octreotide	KCl	K citrate
Kayexelate	tizanidine	naratriptan	

amitriptyline	perphenzaine	imipramine
thioridazine	fluphenazine	trifluoperazine
cimetidine	promethazine	doxepin
chlorpromazine	nortriptyline	quinine
troleandomycin	maprotiline	indinavir
ritonavir	pentamidine	chloroquine
tetracyclic antidepressants		opioids

Drugs Withdrawn from Market Due to QTc Effect

Terodiline	GU
Terfenadine	Antihistamine
Astemizole	Antihistamine
Sertindole	CNS
Grepafloxacin	Antibiotic
Droperidol	CNS
Cisapride	GI

The evolution of the E14 document



The ICH E14 Guidance Document

- The ECG and QT prolongation are imperfect biomarkers of proarrhythmic risk
  - There is a "qualitative" relationship between QT prolongation and TdP
- Both clinical and non-clinical data will be used to make an integrated assessment of proarrhythmic risk
- All new candidates with systemic bioavailability regardless of therapeutic indication/area should have a "thorough QT/ QTC" study, and also existing approved products, if there is a new dose, route of administration, indication or patient population

The E14 Paper: Key Points -1

- All drug candidates with systemic bioavailability should have a thorough clinical evaluation for potential QT prolonging effects regardless of Pre-clinical data
- All drug candidates should be assessed at sustainable multiples of the anticipated maximum therapeutic concentrations
- The study should demonstrate that it has ability to detect QT/QTc prolongation by the use of a concurrent positive control group alongside a placebo group

The E14 Paper: Key Points -2

- A "Thorough QT/QTc" study is typically conducted early in the clinical development process
- The study should be designed to allow detection of
  - Time matched mean difference between drug and placebo
  - QTc interval difference "around 5 msec" with a 95% confidence interval that excludes an effect of >10 msec
- In order to reduce variability multiple ECG collection is recommended for each matched time point for the thorough QT/QTc study

The E14 Paper: Key Points -3

- ECG's should be measured by a few skilled readers operating from a centralized ECG Laboratory, and the reader may be assisted by a computer
- Readers should be blinded to time, treatment subject identifier and one reader should read the ECGs from a single patient
- The degree of intra- and inter-rater variability should be established, and, in multi-center trials, all machines need to be calibrated and consistent and site personnel need to be well trained to assure consistency

The E14 Paper: Key Points -4

- If the thorough QT/QTc study shows an absence of QT/QTc prolongation then subsequent studies can be collected in accordance with current standard investigational practices

- If the thorough QT/QTc study is positive then additional ECG safety evaluation is required in Phase 2 and 3

Correction of QT

- Types of QT corrections (all dose groups):
  - Required:
    - QTcB: Bazett's, $QTc=QT/RR^{1/2}$
    - QTcF: Fridericia's, $QTc=QT/RR^{1/3}$
  - Optional:
    - Linear regression (e.g. Framingham)
    - Population based linear or non-linear regressions
    - QTcI: Individual corrections based on regression analysis on serial baseline recordings

Statistical Analysis of QT/QTc

- Central tendency analysis
  - Time matched
  - Time averaged
  - C max
- Categorical/outlier analysis
    - Absolute value >450 msec
    - Absolute value >480 msec
    - Absolute value >500 msec
    - Change from baseline >30 msec
    - Change from baseline >60 msec

Safety Analysis

- AEs of interest:
  - Torsades de Pointes
  - Ventricular tachycardia, arrhythmia, ectopy, fibrillation and flutter
  - Cardiac arrest
  - Sudden death
  - Syncope
  - Dizziness
  - Seizures
- Assessed in the population intended to be treated as well as any applicable special populations
- Followed through post-marketing safety surveillance

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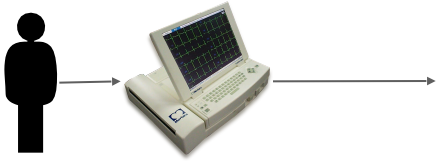
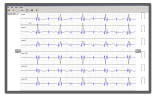
Digital ECG Lifecycle

Investigators site



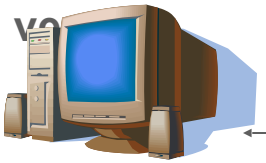
Acquire ECG



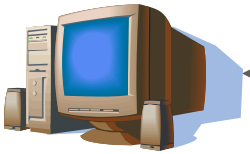
Digital ECG

- Digital ECG report
- Automatic interpretation
- ECG criteria check

ECG v



- ECG Reception Server



- ECG safety check
- ECG quality check
- ECG analysis
- ECG criteria check

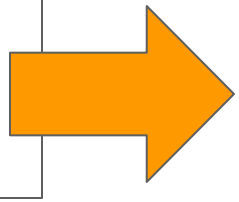
- Query resolution

- Data cleansing
- Data validation

Sponsor

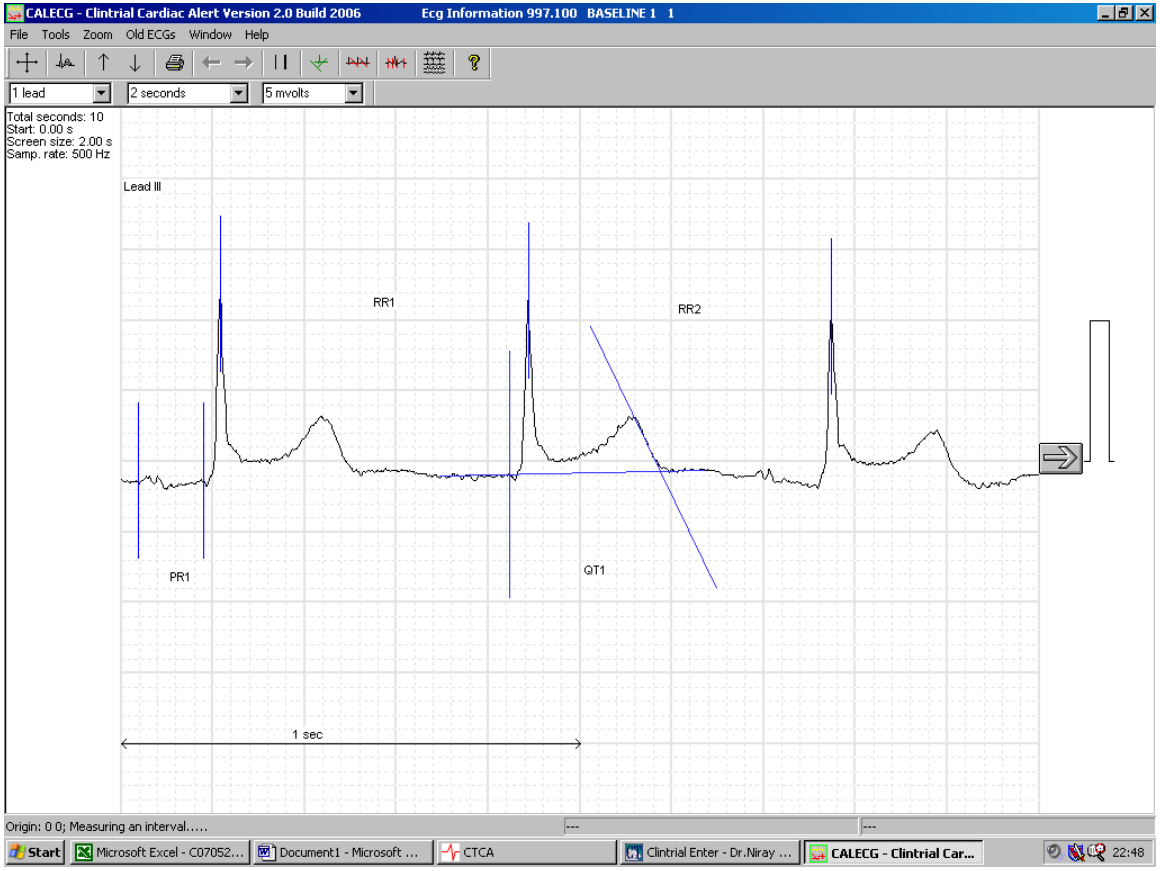
- Query resolution

- Data cleansing
- Data validation



FDA

ECG Measurement (QT Interval)



- Multiple measurements made
- Accuracy of 1 ms on computer screen
- This is 1/40th of a mm on a usual ECG recording at 25 mm/sec
- An investigator reading an ECG can't be accurate to more than 10 ms (1/4th mm)

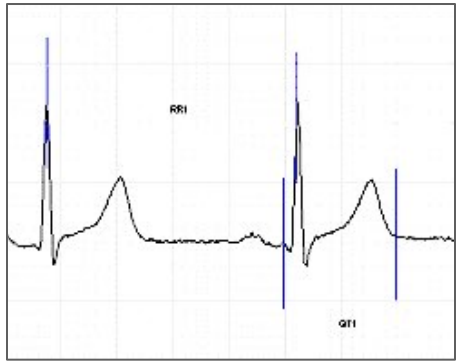
Interval and duration measurement methodology

- On screen calipers
- Threshold method or tangent method
- Manual or Semi-automated
- Average 3-5 QT values per ECG
- Observer blinded to patient identifier, age, time of ECG collection, therapy group
  - Can't be blinded to age or gender if age or gender-specific criteria used
- Single Median Beat or Automated Analysis are being evaluated

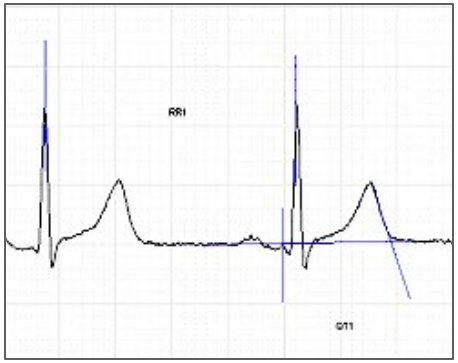
Comparison of QT measurement by tangent method and threshold method

Presented at: 58th Annual Cardiological Society of India Conference,New Delhi, India,December 8-10, 2006

- **Most problems due to difficulty in identifying end of T wave**
- **2 methods – some believe tangent to be more objective**



Threshold method - intersection of the terminal limb of T wave and the isoelectric baseline



Tangent method – Intersection of line drawn from the peak of T wave to the point of maximum slope on the terminal limb of the T wave and the baseline.

- **To study the differences in QT interval by threshold and tangent methods**
- **To see which method is more objective (less intra-reader variability)**

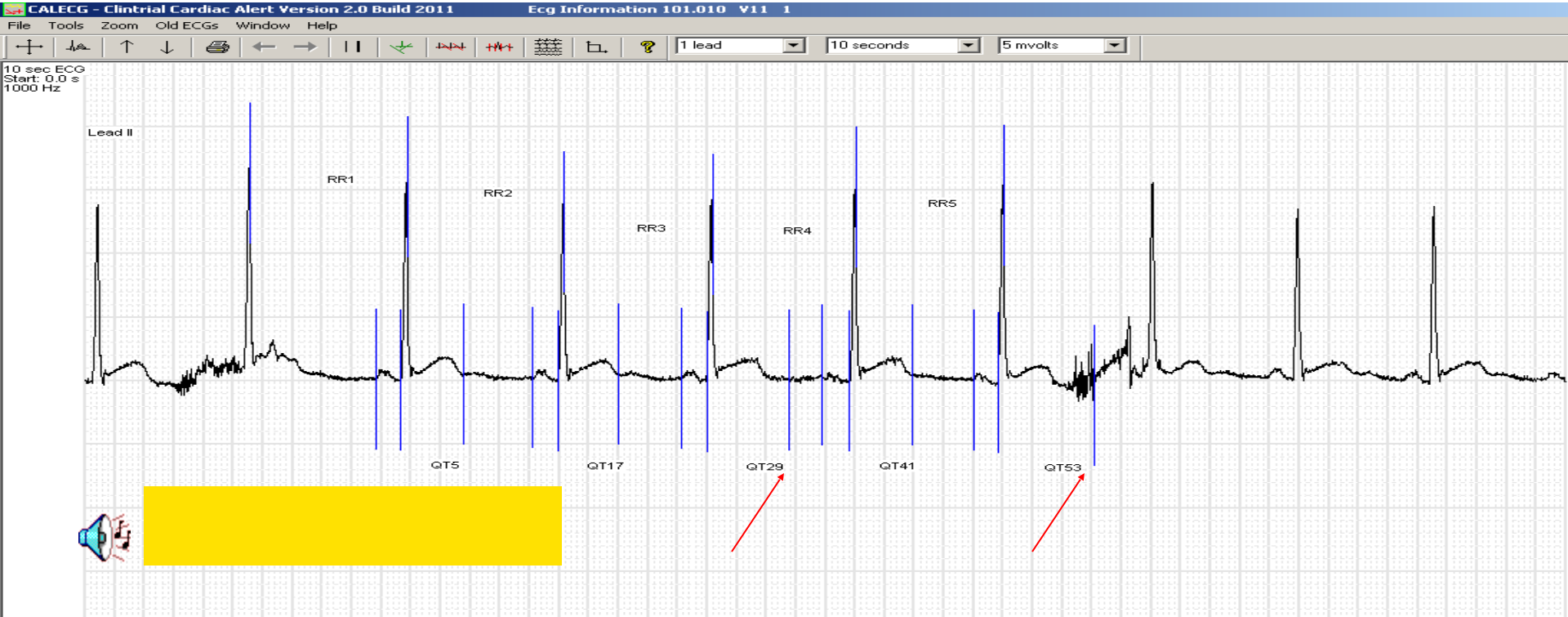
Threshold vs. Tangent

- 100 ECGs read twice by 8 experienced readers
- By threshold and tangent Methods

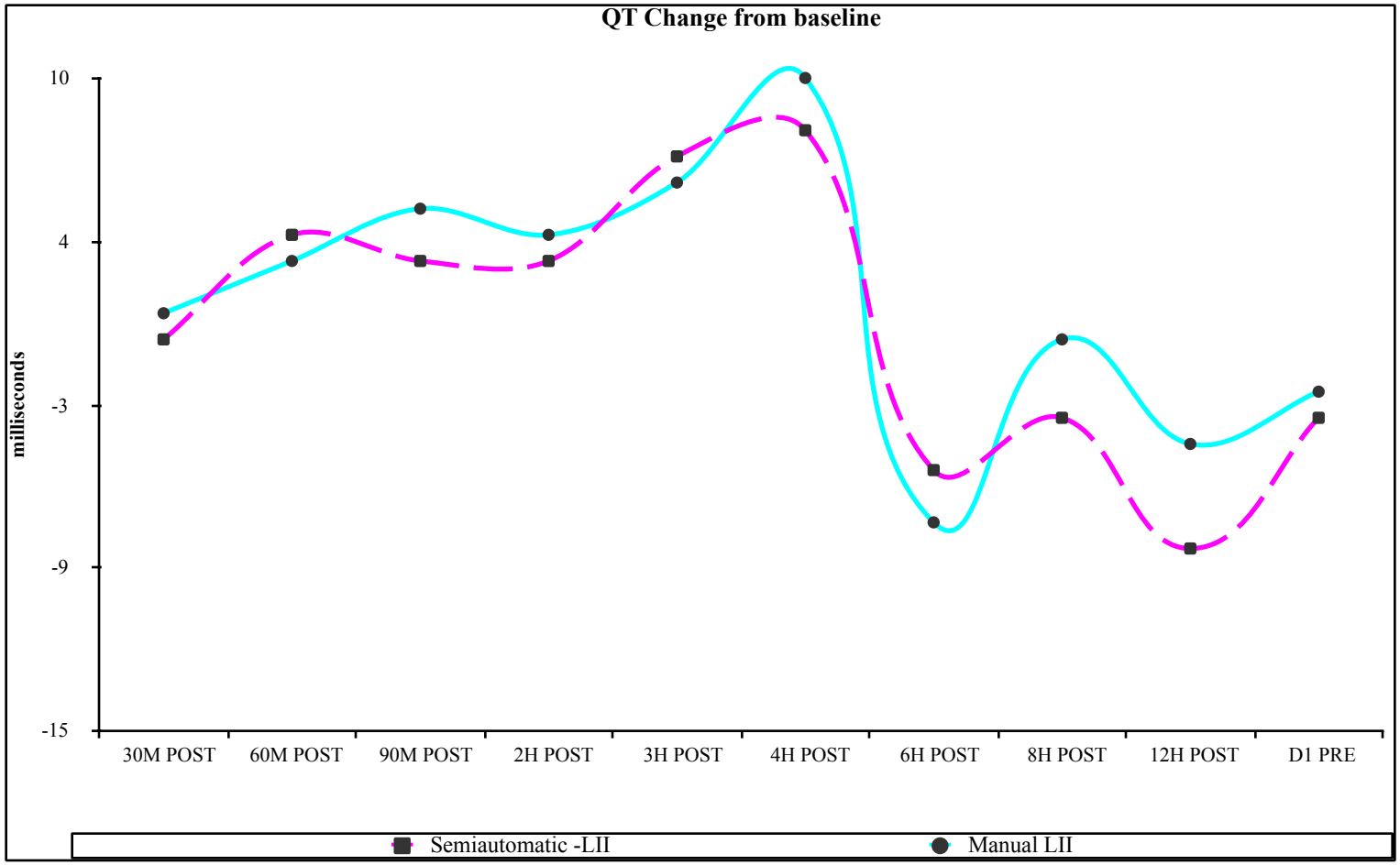
RESULTS	QT interval (ms)		
	Manual (Mean ± SD)	Automated (Mean ± SD)	P value (Manual vs Automated)
Threshold	392±14 ms	400±19 ms	<0.001
Tangent	382±14 ms	357±19 ms	<0.001
P value (Tangent vs Threshold)	<0.001	<0.001	

- Intra-reader variability for the manual threshold method **6 ± 5 ms (-4, 16 ms)**
- Intra-reader variability for the manual tangent method **6 ± 5 ms (-4, 16 ms)**

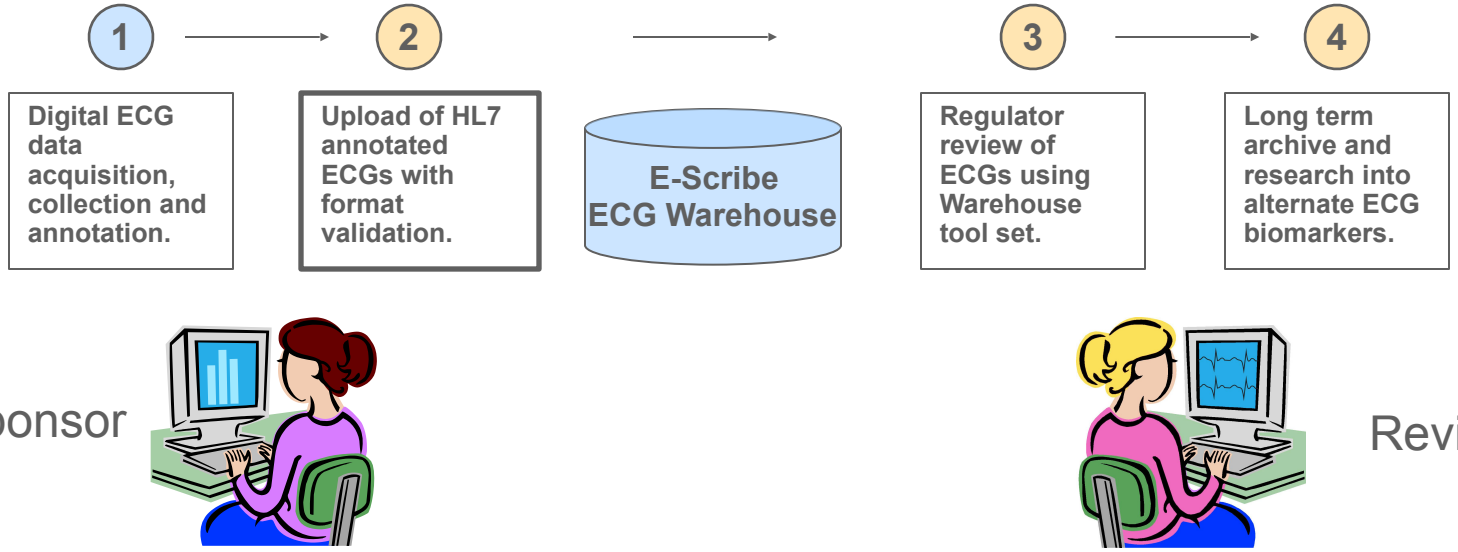

CALECG - Clintrial Cardiac Alert Version 2.0 Build 2011
Ecg Information 100.010 V11 1
File Tools Zoom Old ECGs Window Help
1 lead
10 seconds
5 mvolts
10 sec ECG
Start: 0.0 s
1000 Hz
RR1
RR2
RR3
RR4
RR5
QT5
QT17
QT29
QT41
QT53


CALECG - Clintrial Cardiac Alert Version 2.0 Build 2011
Ecg Information 101.010 V11 1
File Tools Zoom Old ECGs Window Help
1 lead
10 seconds
5 mvolts
10 sec ECG
Start: 0.0 s
1000 Hz
Lead II
RR1
RR2
RR3
RR4
RR5
QT5
QT17
QT29
QT41
QT53

Manual versus Semi-Automated



Providing aECGs for FDA Review – New Method



- Annotated HL7 ECG data sets supporting NDAs uploaded by ECG Core Lab/ Sponsor *free of charge*
- Facilitates regulatory review using tool set provided by Mortara Instrument
- Results in large digital collection of aECGs for future research

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Different designs for tQT studies

- 4 period crossover
  - Placebo, Low Dose, High Dose, Active Control
- 4 way parallel
- 3 way parallel
  - Placebo, Low to High Dose, Active Control
- 3 way crossover
  - Placebo, High Dose, Active Control
- 5-6 way crossover
  - Add Other Approved Agents to show non-inferiority (Insurance!)
- 2 Phase studies
  - Placebo vs Active followed by Low dose, High Dose, Placebo in crossover or parallel design

Issues with QT studies in Oncology

- Can't use healthy volunteers
- Patients are older and sicker with more QT variability hence sample size is higher
- Difficulties with extended placebo or active control
- Patients want active therapy
- Regulatory tolerance of QT effect may be more
- Need to ensure other cardiac side effects (ischemia, cardiomyopathy) is also monitored

- Need more Phase I ECG data (both for QT variability and estimate of QT effect)
- Best design is probably a 2 phase (placebo versus moxi) followed by drug versus standard chemotherapy

Optimum number of replicate ECGs at each time point in a 'Thorough QT' study

Presented at: **DIA "QT Issues on Drug Development" April 12-13, 2007.Washington DC**

Background:

- Several replicate ECGs recorded in thorough QT studies to reduce within-subject variability
- Decreases the study sample size but increases the cost of ECG analysis

Objective:

- To identify the most cost-effective number of ECG replicates

Method:

Analysis of moxi and placebo data of a tQT, 40 subjects, 7 timepoints, 6 replicates

Results

Placebo-subtracted Mean change from Time-matched baseline following 400 mg Moxifloxacin in 40 subjects

	QTcB					
	Replicates					
Time-Points	**1**	**2**	**3**	**4**	**5**	**6**
Pre	-8	0	-2	-1	-1	-1
0.5 HR POD	2	3	4	4	5	5
1 HR POD	12	13	11	12	12	12
1.5 HR POD	10	11	11	11	10	10
2 HR POD	10	8	8	8	8	9
4 HR POD	12	10	10	11	10	10
6 HR POD	6	4	4	3	3	3

- Statistically significant results are highlighted in yellow.
- ΔΔQTcB was statistically significant at 4 time-points with 1,2,3,4,5,6 replicates

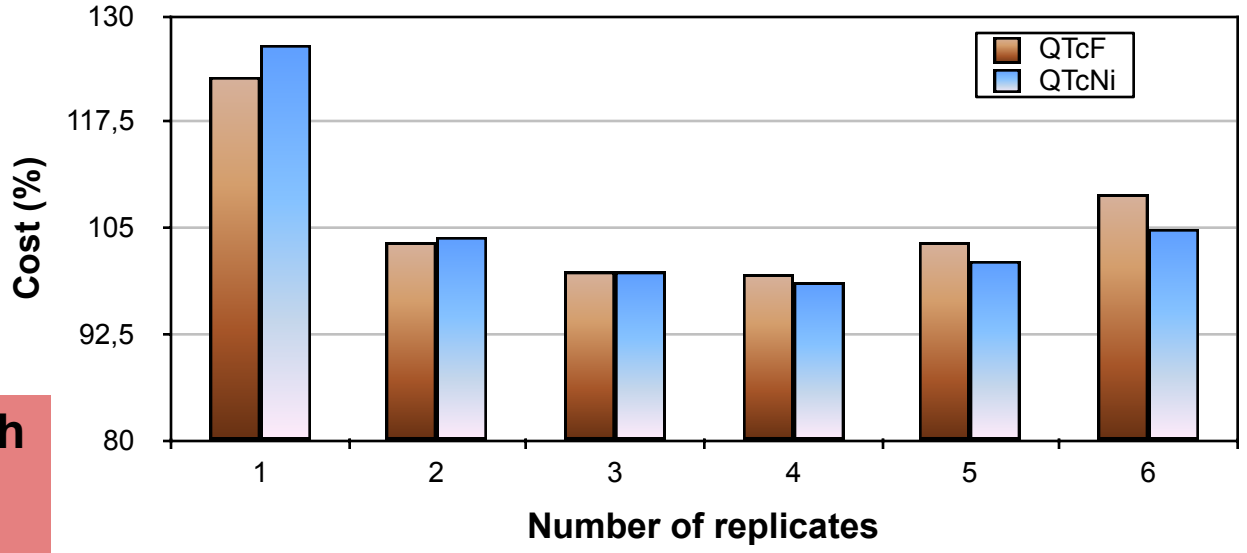
Replicates vs. SD and sample size

Within-subject SD (√MSE) in ms for change from baseline in QTc and sample size for a cross-over TQT study

Replicate Of ECGs	QTcB		QTcF		QTcN		QTcNi	
	√MSE (ms)	Sample Size	√MSE (ms)	Sample Size	√MSE (ms)	Sample Size	√MSE (ms)	Sample Size
1	12.1	100	10.2	71	10.2	71	10.9	81
2	9.2	58	8.5	49	8.5	50	9.0	55
3	8.6	50	7.9	43	7.9	43	8.3	47
4	8.0	43	7.5	39	7.6	39	7.9	42
5	7.8	42	7.4	38	7.5	38	7.7	40
6	7.7	40	7.4	38	7.4	38	7.6	39

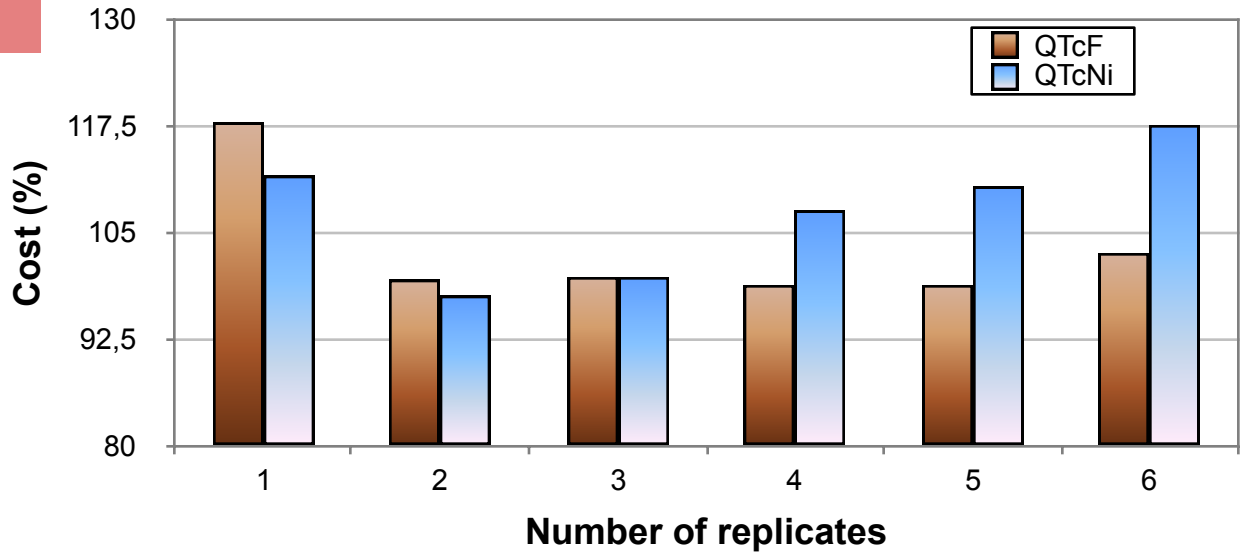
Cost of tQT study with 1 to 6 replicates

Cross-over study



Cost of study with 3 replicates was assumed to be 100%

Parallel study



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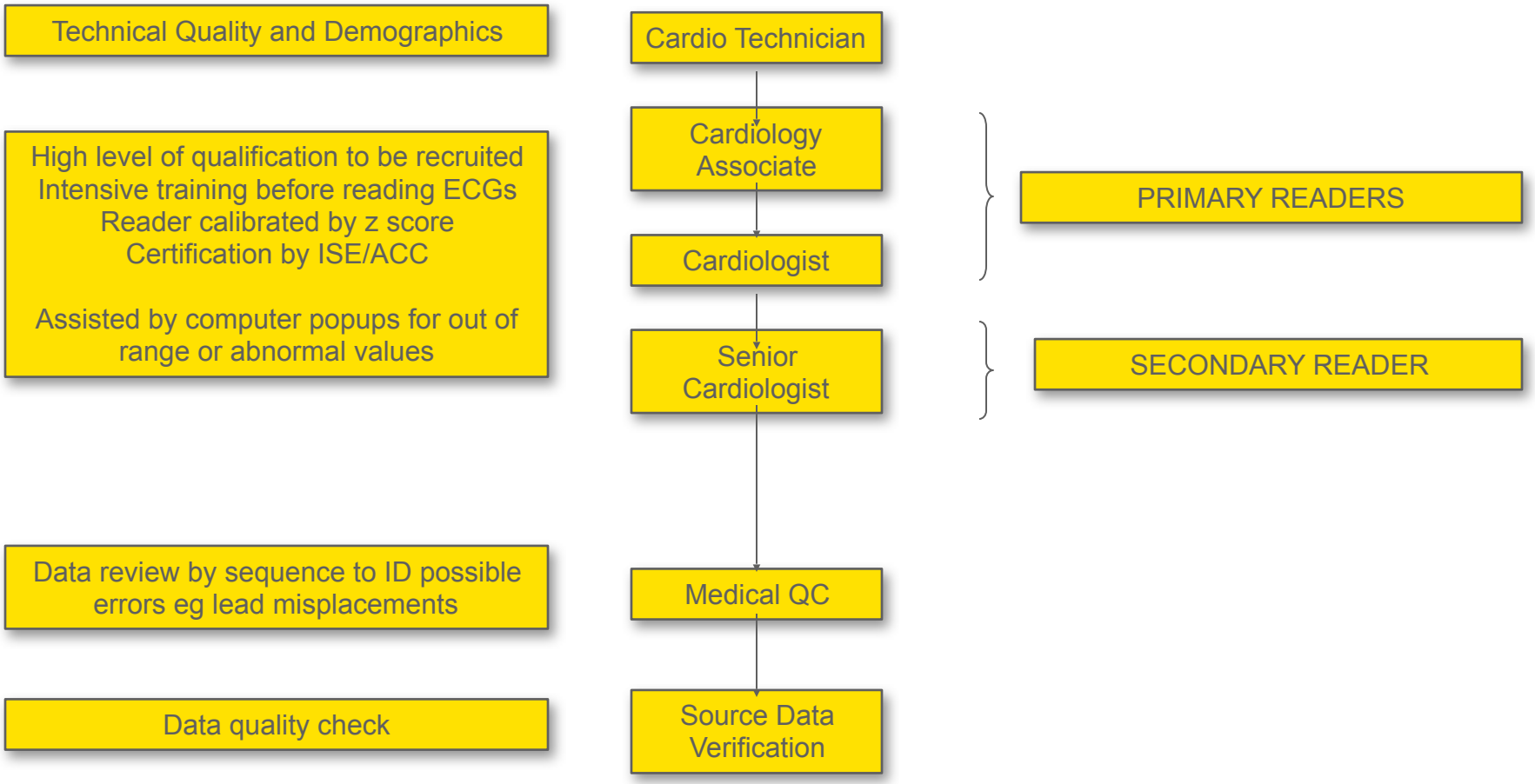
Quality by Process Flow

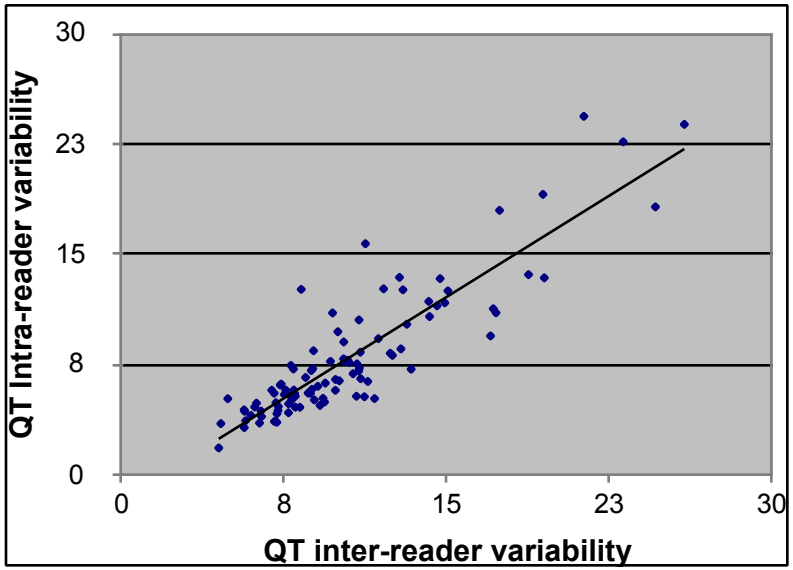


Problems with Intra- and Inter-Reader Variability

- Recommended by E14
- Doesn’t take into account variability due to ECG signal quality or the shape of the T wave
- Current methods are limited in their ability to compare multiple readers in a large core laboratory

Do ECG characteristics predict variability in QT measurements in clinical trials?

Presented at: **57th Annual Cardiological Society of India Conference,Mumbai, India December, 2005**



ECGs with large inter-reader variability also had large intra-reader variability. Therefore values cannot be compared with different ECG datasets.

It's the T-Wave amplitude

Distribution of T wave amplitude in 950 ECGs demonstrates that most ECGs lay between 1mm to 5mm

Mean and SD of intra-reader variability for each T-wave amplitude

T wave amplitude	0-1	1.01-2	2.01-3	3.01-4	4.01-5	5.01-6	6.01-7	>7
N	33	171	216	240	170	67	18	20
Mean variability	**11**	**10**	7	8	7	8	8	7
SD	7.2	8.4	6.1	5.4	5.3	5.8	4.3	4.3

- Only abnormal T wave morphology to show high reader variability were notched T waves (the mean amplitude was 0.85 mm for notched T waves)
- For biphasic and inverted T waves no significant difference in reader variability was noted as compared to the normal T waves

z score or standardized deviate

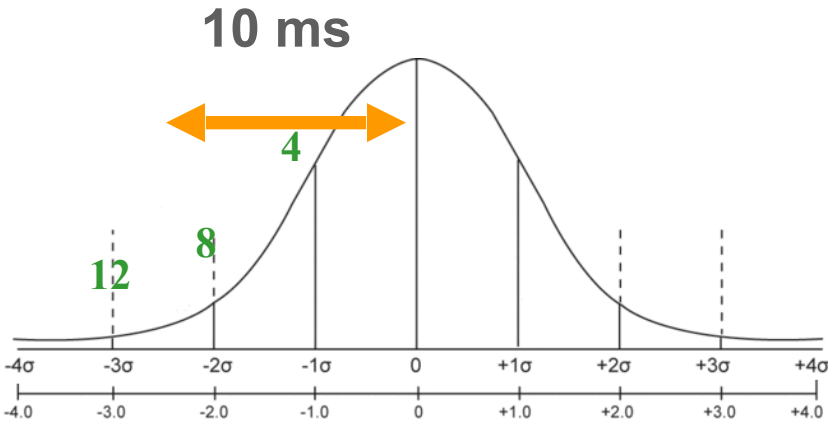
z score is difference between reader's measurement and mean, in terms of 'SD' units

Z = (QTreader – QTmean)/SD

Example 1

QTreader = 390 ms
QTmean = 400ms
SD = 4ms

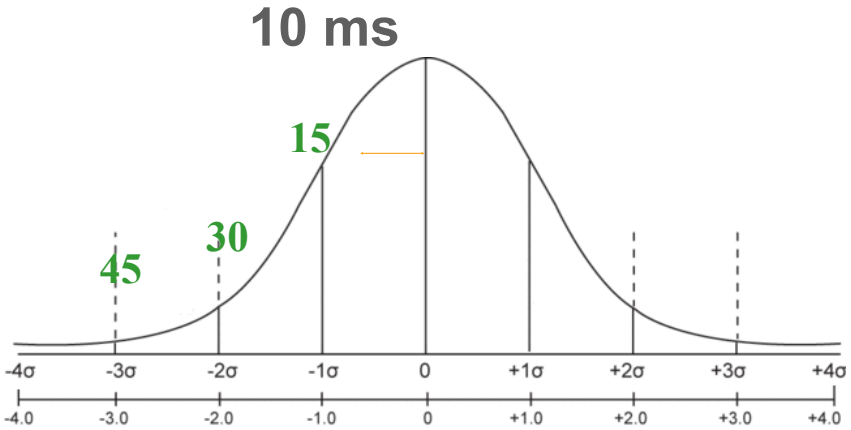
z = (390 – 400)/4 = 2.5



Example 2

QTreader = 390 ms
QTmean = 400ms
SD = 15ms

z = (390 – 400)/15 = 0.67

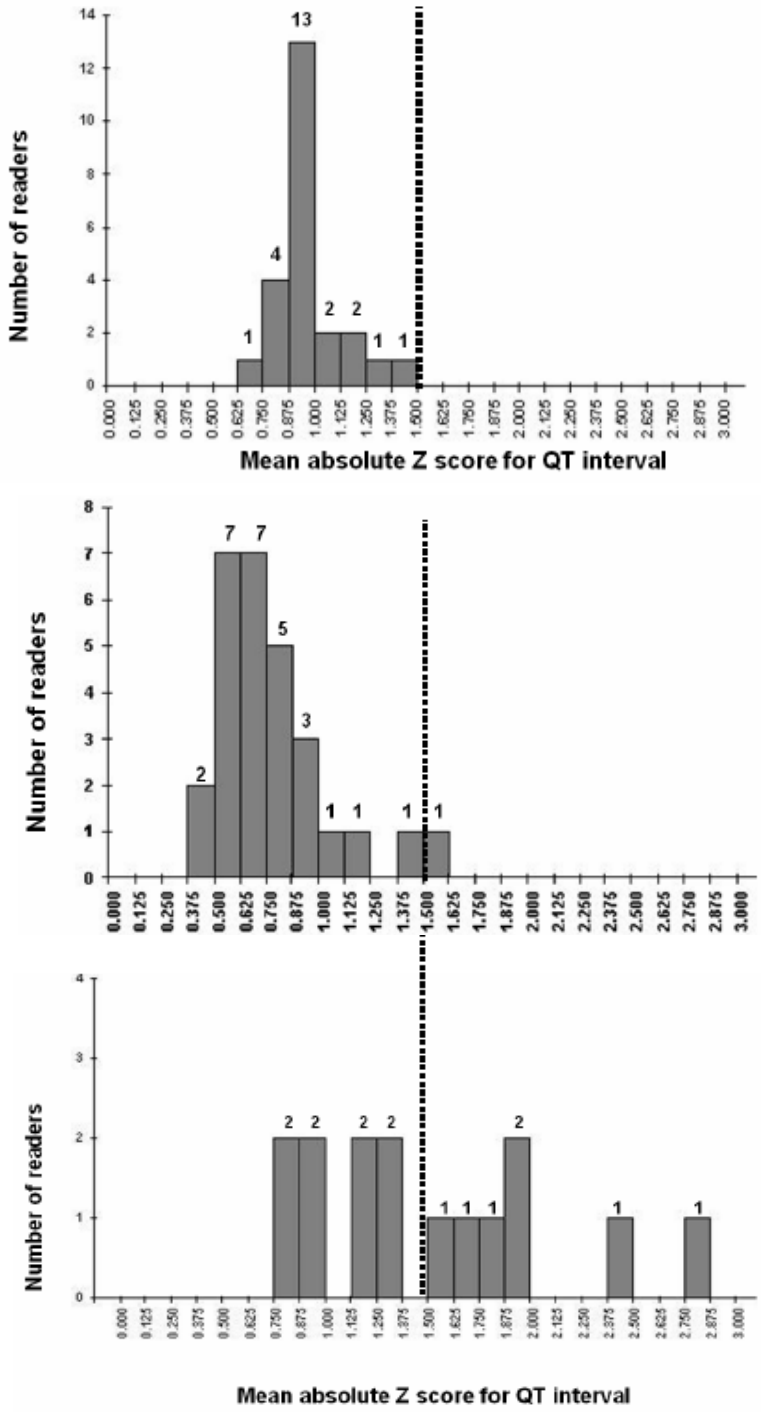


Distribution of mean absolute Z scores of QT interval measurements by readers using a set of 100 digital ECGs

(A) Z scores of expert readers (n=24) whose measurements were used to develop a cut-off value for an acceptable z score Based on this histogram, a z score of ≤1.5 was considered to be acceptable.

(B) Z scores of trained readers (n=28) working in the laboratory – one reader had z score >1.5. The histogram moves to the left (better)

(C) Z scores of new readers (n=15) after structured training were widely scattered and only 8 readers had z scores ≤ 1.5



Evaluation of new readers during training

Number of new readers evaluated from Jan 2006	15
Readers with mean z score ≤1.5	8
Readers with mean z score >1.5	7

Reader	Z score evaluation results		
1	1.7	1.2	
2	1.8	1.9	0.9
3	1.9	0.8	
4	2.8	2.0	1.4
5	1.9	0.9	
6	1.6	0.7	
7	2.4	1.1	

The Metrics Consortium and the FDA Warehouse

- MCC is an open, multidisciplinary, non-profit organization committed to the development of worldwide industry standards

- Examples:
  - Percentage of ECGs reported within agreed turnaround time
  - Percentage of on-time equipment shipments to sites

- FDA/Mortara warehouse has measurable metrics of ECG and annotation quality but utility remains restricted as methods are proprietary

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Trends

- Move to digital ECG collection and storage for all phases of a clinical program
- Increased focus on results of preclinical data and intensive ECG collection in early Phase I studies to make strategic go/no go decisions
- Development of other biomarkers for drug-induced QT prolongation (eg T-wave residua)
  - Restricted by lack of gold standard data from problem drugs

Thank you

Questions? dhiraj.narula@quintiles.com