

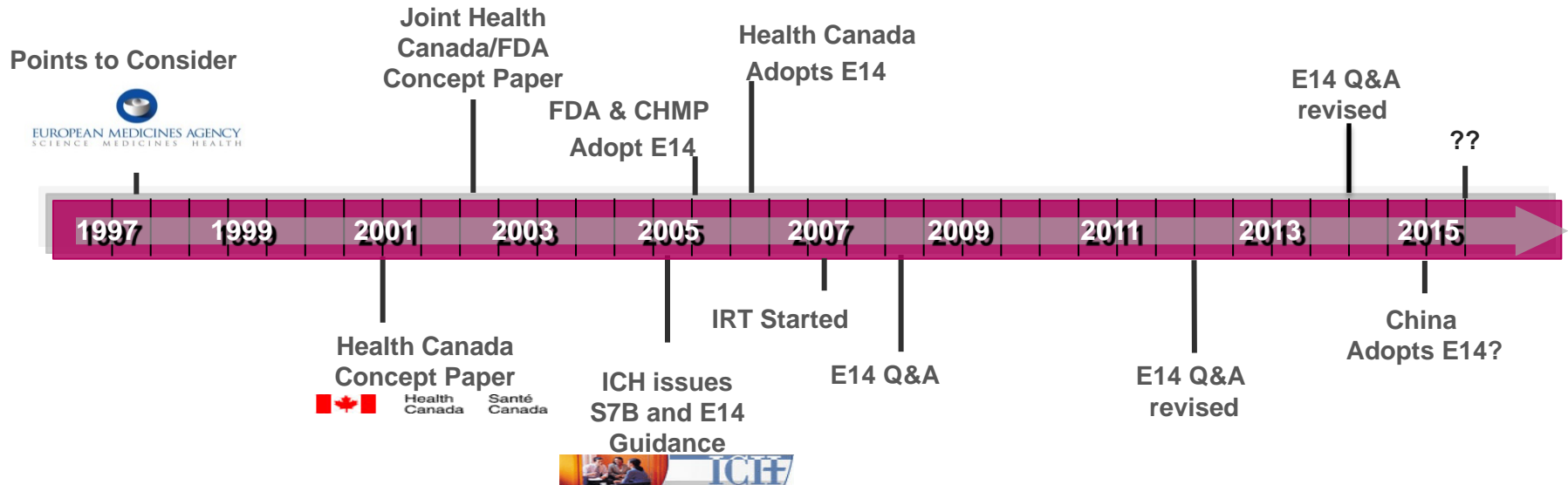


# **QT Assessment: The new paradigm, but now what?**

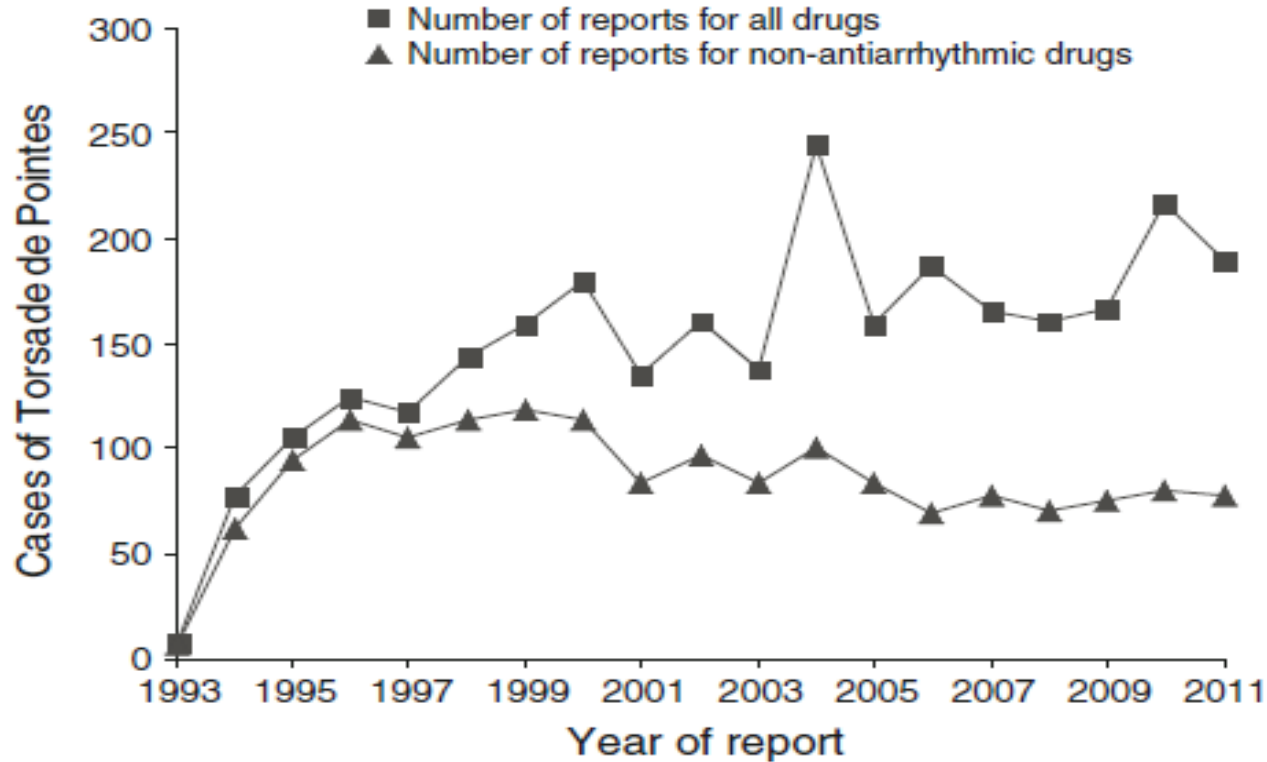
Joy Olbertz PharmD, PhD

Senior Director, Cardiovascular Safety Services

# The Evolution of ICH E14



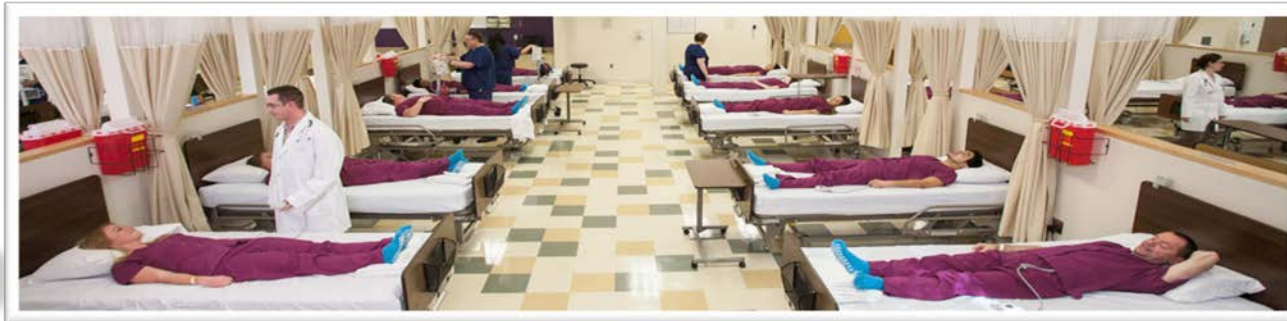
# Cases of Torsades de Pointes



Annual number of spontaneous reports of Torsade de Pointes received by the US FDA Adverse Event Reporting System, Stockbridge et al. Drug Safety 2013;36:167-182

# The Future of ICH E14

- Movement to assess QT prolongation risk in early clinical studies rather than a dedicated TQT
- IQ-CSRC study completed to provide scientific rationale for this approach
  - International Consortium for Innovation & Quality in Pharmaceutical Development (IQ)
  - Cardiac Safety Research Consortium (CSRC)
- Likely not revising ICH E14 but rather updating the Q&A

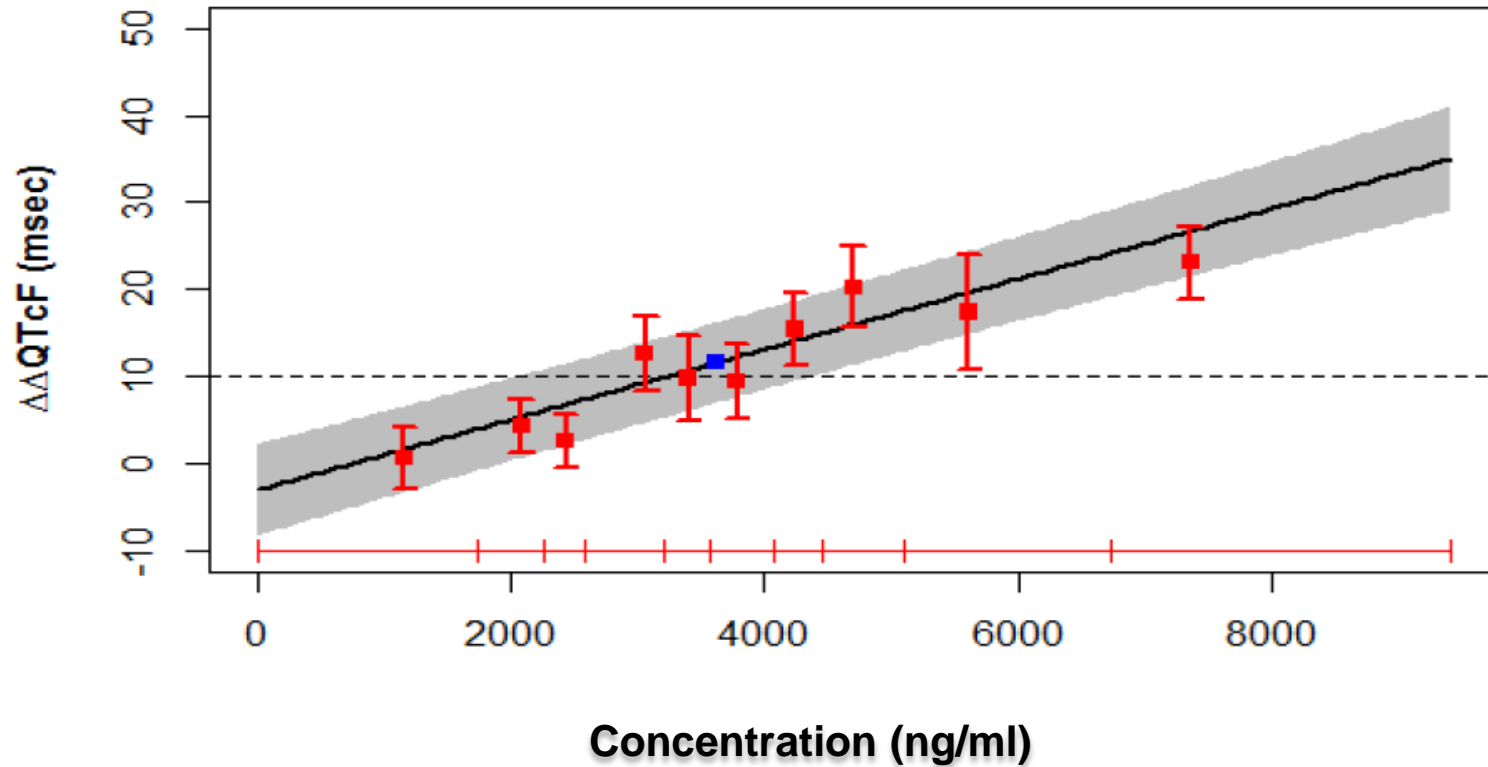


# IQ-CSRC Study

- 3 period, randomized, placebo-controlled study
- 20 healthy subjects
- 6 study drugs: 5 “QTc-positive”, 1 “QTc-negative”
- Incomplete block design used
  - Each study drug administered to 9 subjects and placebo to 6
- Exposure response analysis performed
  - Evaluate relationship between plasma concentration and placebo corrected, change-from-baseline QTc ( $\Delta\Delta\text{QTc}$ )
- “QT positive” if the UB of the 2-sided 90% CI of the predicted placebo-corrected  $\Delta\text{QTcF}$  is above 10 ms at the observed geometric mean  $C_{\text{max}}$  of the lower dose of the studied drugs

# IQ-CSRC Study

## Quinine



# Intense ECG Data Collection in Early Studies

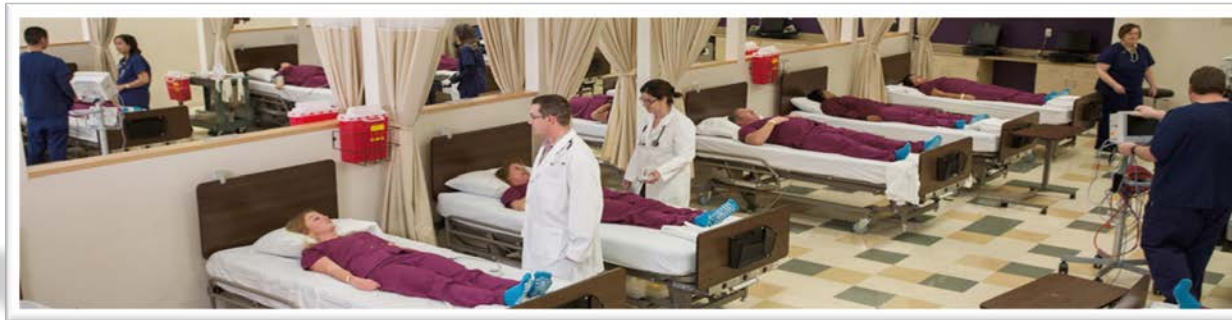
- TQT “like” ECG data collection
  - Holter monitors
  - Triplicate measurements
  - Baseline and post-dose ECG extractions
  - Low data variability is key
- Data collected at **multiple dose levels** then exposure response (QTcF/PK) modelling performed to determine trend if any for QTcF prolongation





# Sounds Promising but...

- When I go to submit my TQT waiver what will be required for my preclinical package?
- How high does the SAD or MAD dose need to be? How does this impact the potential success of my TQT waiver?
- I want to add a patient cohort to the end of my SAD/MAD study. Should I include intense ECG monitoring?
- I am uncertain that early TQT like data collection is the right fit for my program, do I have to do this?





# **Comparison of Semi-Automated vs. Highly Automated ECG Analysis**

# Objective

- Automation suggests the potential for data sets with reduced variability and consequently, greater power per subject vs. the SA method
- Can Highly Automated (HA) methodology give results similar to Semi-automated (SA) methods?



# Overview



- Five vendors participated, using three ECG analysis algorithms – unknown to each other
- Semi-automated (SA): ECG interval measurements are all reviewed and confirmed by a cardiologist
- Highly automated (HA): Varied methods were used to extract and measure ECG interval measurements with the majority of interval measurements automated with some varying degree of cardiologist oversight

# Methods

- Vendors were supplied raw Holter data from a TQT study previously analyzed using SA approach
- Analysis assessed:
  - Scientific validity of the vendor algorithm (alignment with prior SA analysis)
  - Variability of key ECG parameter intervals
  - Overall rank order of vendor performance at these tasks as judged by Clinical Utility Index



# Conclusions

- All automated QTc analysis results aligned to the SA analysis results
  - Systematic differences in the absolute value of raw data do not substantially alter outcome across all effect sizes
    - Unlikely to have a false positive result for small drug effects
    - Unlikely to have a false negative result for marginal moxi effects
- SA analysis is analytically competitive with HA analysis
  - Variability was similar so HA methodology does not necessarily reduce enrollment needs
  - However, typically timelines are longer and costs higher with SA
- Vendor rankings identified by CUI were based on small differences

# Automated ECG Analysis



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Journal of Electrocardiology 46 (2013) 118–125

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## Pattern recognition analysis of digital ECGs: Decreased QT measurement error and improved precision compared to semi-automated methods<sup>☆</sup>

Olivier Meyer, MS,<sup>a,\*</sup> Georg Ferber, PhD,<sup>b</sup> Gerard Greig, MD,<sup>c</sup> Henry H. Holzgrefe, BA<sup>c</sup>

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<sup>b</sup>Statistik Georg Ferber GmbH, Riehen, Switzerland

<sup>c</sup>Clinical Pharmacology, F. Hoffmann-La Roche, Basel, Switzerland

<sup>d</sup>Department of Toxicology, Charles River Laboratories, Reno, NV, USA

Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

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Journal of Electrocardiology 46 (2013) 717.e1–717.e9

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## Comparative TQT analysis with three fully-automated platforms Comparison to core laboratory semi-automated results<sup>☆</sup>

Olivier Meyer, MS,<sup>a,\*</sup> Gerard Greig, MD,<sup>b</sup> Henry H. Holzgrefe, BA<sup>c</sup>

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<sup>c</sup>Department of Toxicology, Charles River Laboratories, Reno, NV, USA

*Clinical Pharmacology & Therapeutics* **86**, 503–506 (November 2009) | doi:10.1016/j.cpt.2009.09.011

## Comparison of Manual and Automated Measurements of the QT Interval in Healthy Volunteers: An Analysis of Five Thorough QT Studies

C Fossier, G Duczynski, M Agin, P Wicker and B Darpo

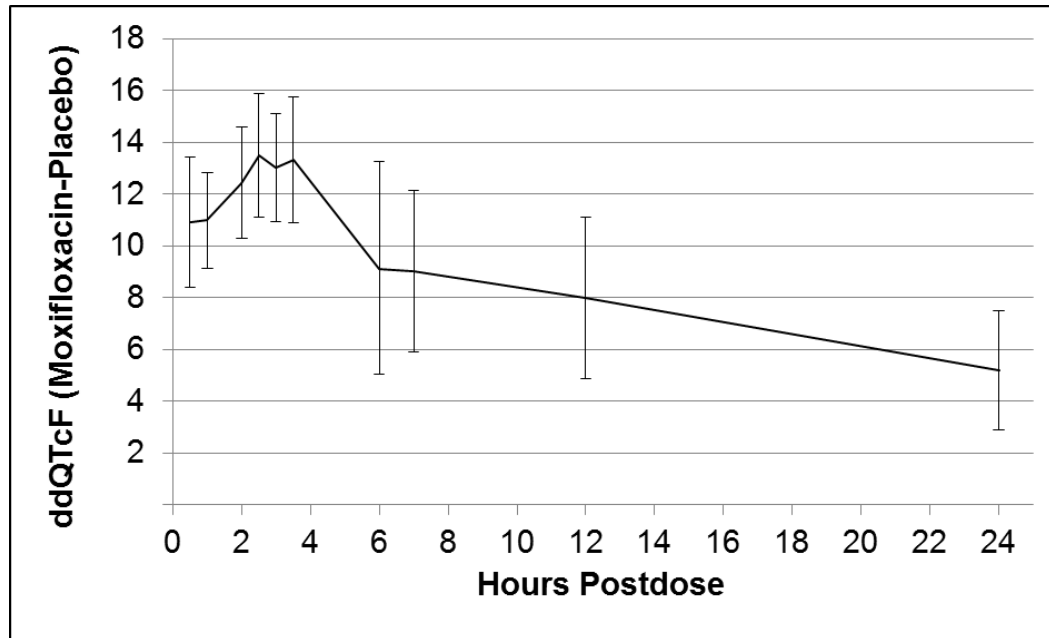
**We analyzed five crossover, thorough QT (TQT) studies to compare automated, manual, and computer-assisted (CA) measurement methods. All the methods detected moxifloxacin-induced, baseline-adjusted, placebo-subtracted mean changes in Fridericia-corrected QT interval (QTcF), with peak effect ranging from 10 to 21 ms. The variability associated with manual and CA measurements was generally 5–28% greater than that associated with automated methods. The performances of automated, manual, and CA measurements were comparable for the purpose of demonstrating assay sensitivity in TQT studies with healthy volunteers.**

**George, S., Rodriguez, I., Ipe, D., Sager, P. T., Gussak, I. and Vajdic, B. (2012), Computerized Extraction of Electrocardiograms From Continuous 12-Lead Holter Recordings Reduces Measurement Variability in a Thorough QT Study. *Journal of Clinical Pharmacy*, 52: 1891–1900.**



# Case Study #1: HA analysis of TQT

Highly Automated and Automated Data has been Accepted by Regulatory Agencies for TQT



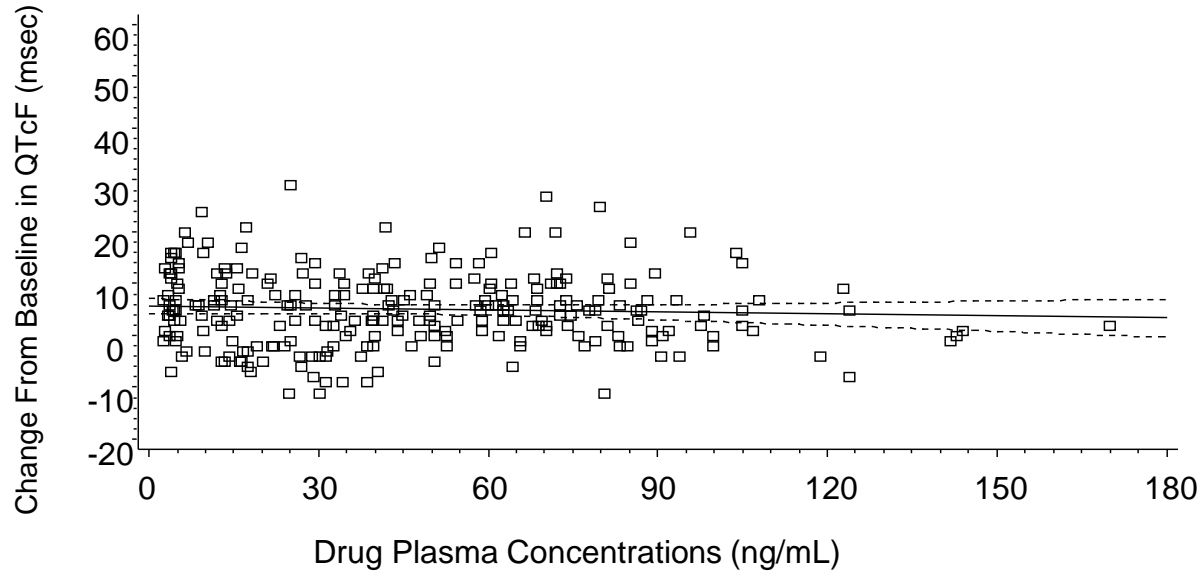
Results from a Thorough QT (TQT) study demonstrating assay sensitivity using moxifloxacin as a positive control. ECG data was analyzed using a highly automated approach in a TQT study with only 36 subjects.

# Case Study #2: HA analysis of DDI study

- Drug-Drug Interaction study (N=16)
  - Period 1: Single dose study drug
  - Period 2: dosing with inducer
  - Period 3: inducer + study drug
- ECG extractions: 3 pre-dose timepoints + 7 post-dose timepoints in Period 1, 2 & 3



# Case Study #2: HA analysis of DDI study



**Slope = -0.01264 (95% CI: -0.039488, 0.014209)**  
**Intercept= 5.60 (95% CI: 4.07, 7.12)**  
**R<sup>2</sup>= 0.0034**

# Questions