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# Mitigating Risk for Cardiac Safety Assessment in Early-Phase Clinical Trials

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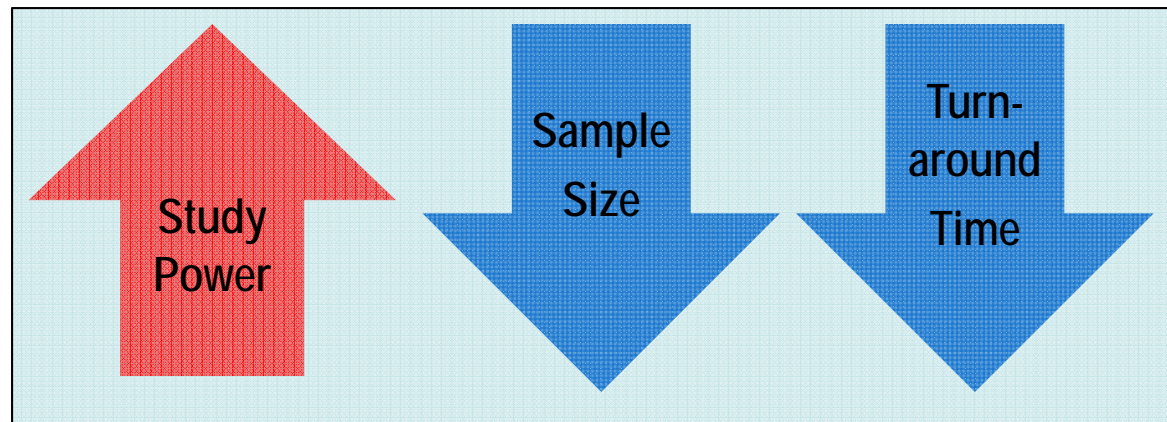
# Objectives

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1. To introduce fully automated 3-D ECG/VCG technology (QTinno)
2. To compare its accuracy, precision, turn-around time, and cost-effectiveness with current modalities in ECG assessment of early cardiac toxicity (TQTS, SAD, MAD) with a special focus on:
  - Automated (Optimized) ECG Extraction from 24-hrs Holter
  - Precision and Accuracy of IDMs (QT/QTc) by QTinno

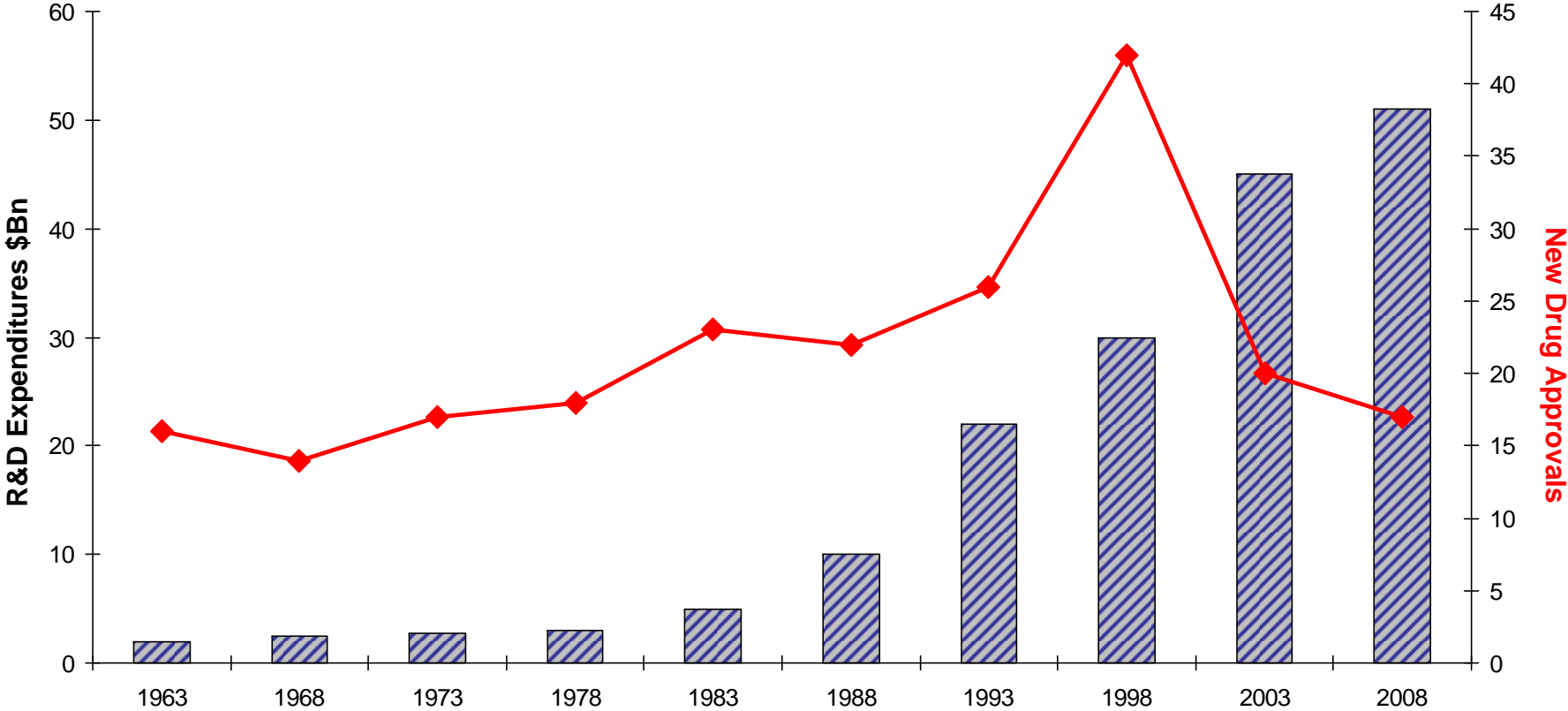
# Why is QTinno a “Disruptive Innovation”?

- Superior Precision, Accuracy, Reproducibility
- Selection (Extraction) of Better Quality Data
- Power of Computing Automation



**Cost Effectiveness**

# New Drug Approvals Are Not Keeping Pace With Rising R&D Spending



Adapted from Kaitin, K. 2010. Clin. Pharmacol. Ther., 87, 356 - 361

# ECG in Early Phases Clinical Trials: Current Practice

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1. Extraction of 3 ECGs around designated time frames from 24-hrs Holter recordings - manually by technicians
2. Selection of consecutive 3 cardiac complexes - manually by technicians
3. IDMs placement and/or adjudication - manually by technicians
4. IDMs verification or adjudication - manually by MDs  
(**semi-automated**)

# Current ECG Practice: Challenges and Limitations

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The precision, accuracy and reproducibility of key cardiac safety measurements in manual or semi-automated methodologies are subjects of:

- Inherent human errors, limited precision and accuracy, substantial intra and inter-reader variability, low reproducibility, and high SD
- Are further compromised by manual selection of ECG tracings as well as selection of limited number of P-QRS-T complexes

Therefore, current manual or semi-automated ECG assessments of cardiac toxicity are

**Expensive, Slow, and Labor-Intensive**

**How About Precision and Accuracy?**

# Target: Precision and Accuracy



High Precision  
Low Accuracy

- 90% Confidence Interval (CI)
- Standard Deviation (SD)
- Variability  
(within and between subjects)



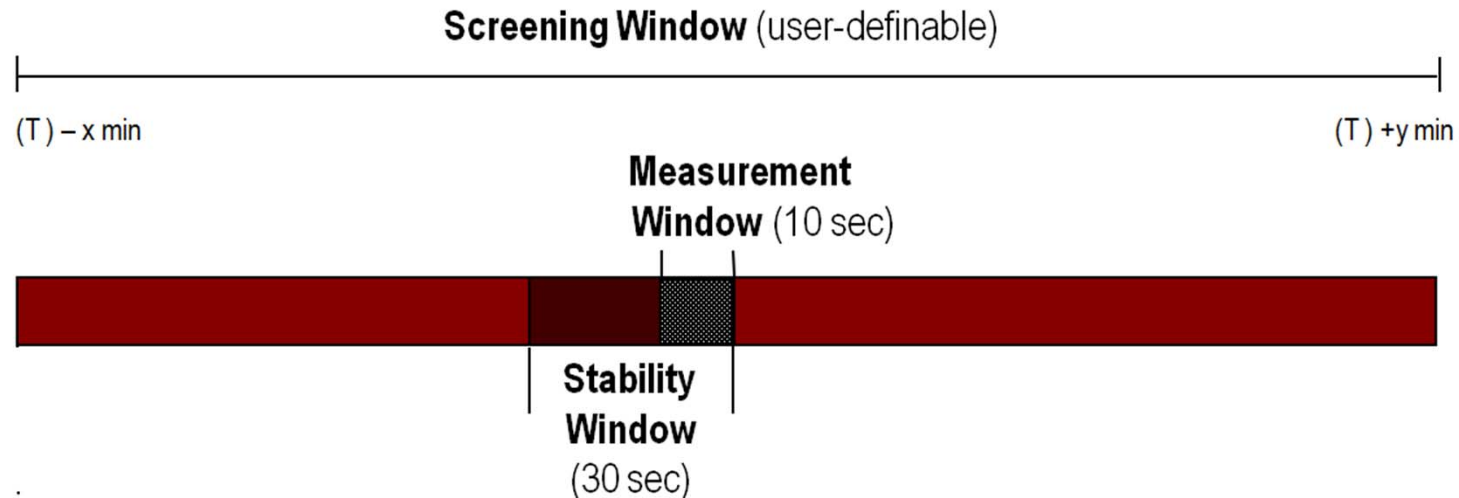
High Accuracy  
Low Precision

- No GS
- “Moxi Signal”  
as a surrogate  
validation tool



High Accuracy  
High Precision

# Optimized ECG Extraction from Holter Recordings\*



Optimized ECG selection through automating the ECG extraction process

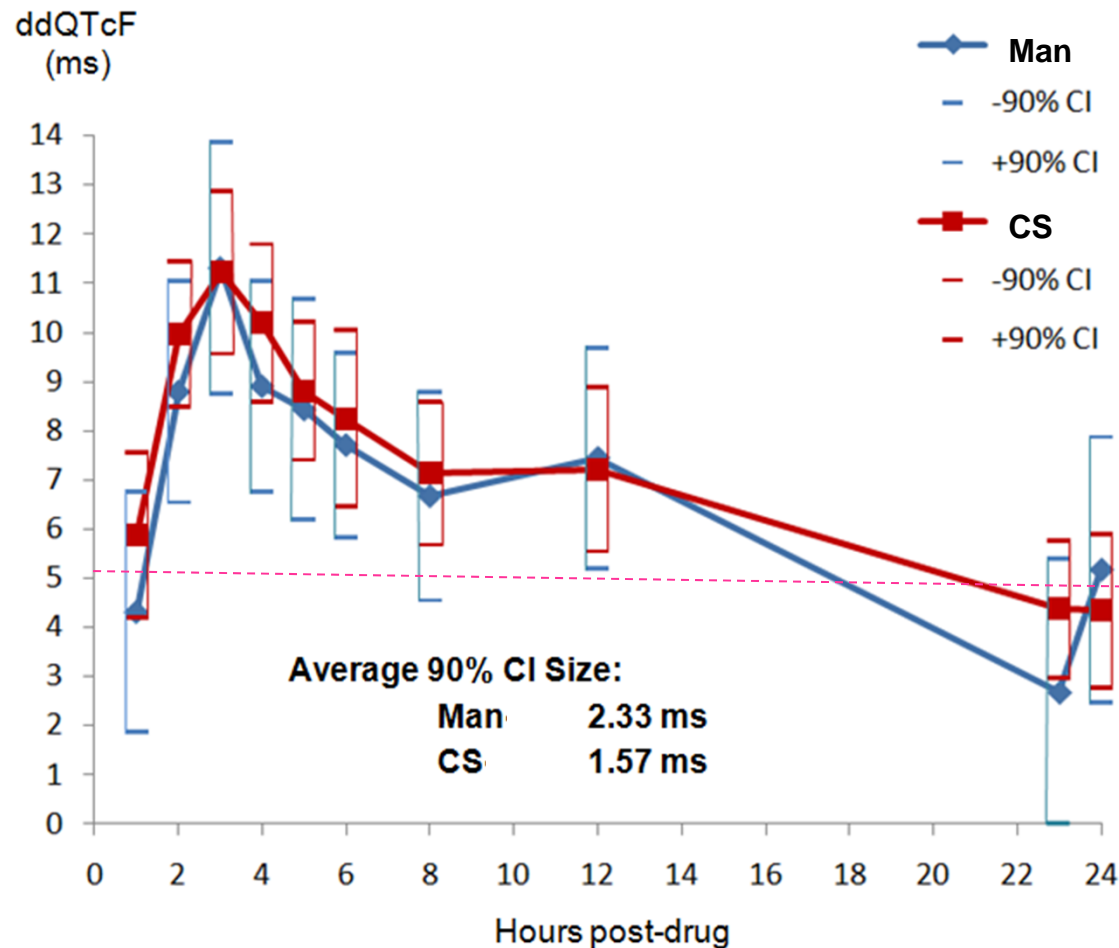
- User defined screening window
- Determines optimal ECGs within screening window
- Ensures reproducibility of ECG extractions

\* - Presented at American Society for Clinical Pharmacology and Therapeutics, 2011

\* - Presented at FDA/DIA Cardiovascular Safety Meeting, 2011

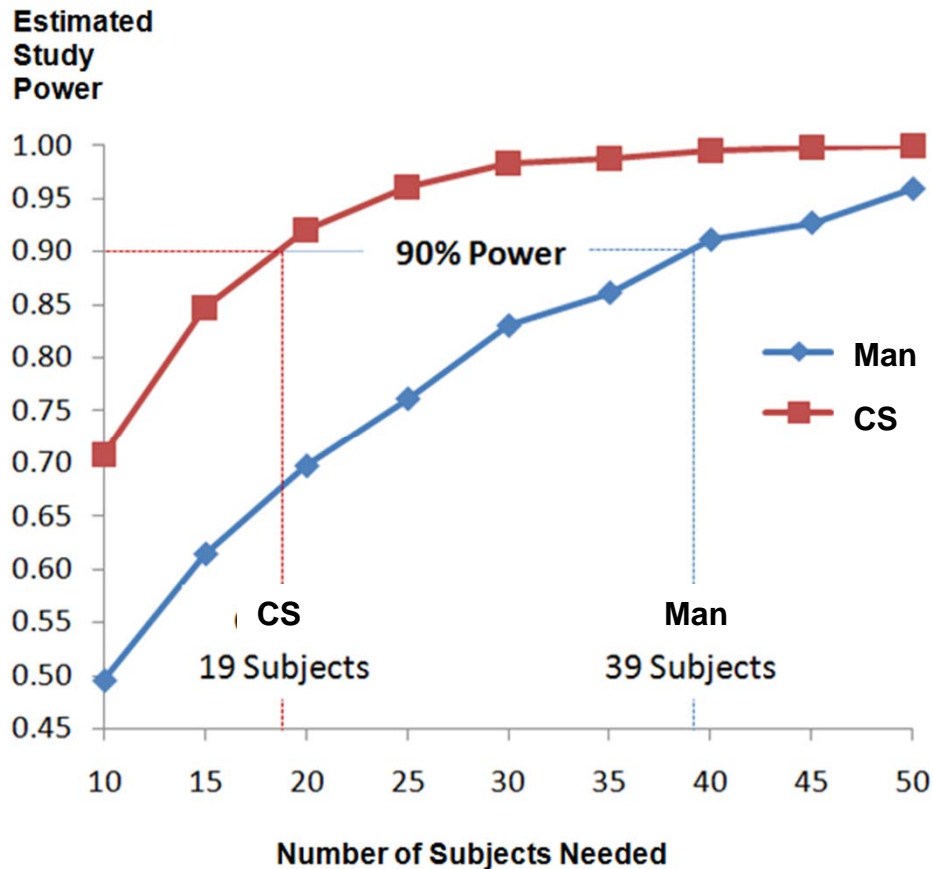
\* - Journal of Electrocardiology, 2011 (article in press)

# Optimized Computer Selection of Optimal ECGs: Effect on Hourly ddQTcF Curves



- Both manual (Man) and computer selection (CS) of ECGs produced typical and valid moxi curves with similar point estimates and multiple time points where the lower 90% CI excluded 5 ms
- However, 90% CI size is on average **33% lower** for computer-selected ECGs, relative to manual selection

# Optimized Computer Selection of Optimal ECGs: Effect on Study Power and Number of Subjects Needed



- For bootstrap analysis:
  - Hourly ddQTcF estimates are calculated for 5000 randomly selected subsets of fewer subjects than the original total.
  - Proportion of simulations where at least one 90% lower CI excludes 5 ms is the estimate of study power for detection of moxi ddQTcF effect
- Computer selection of ECGs substantially increases study power over manual selection, or allows the study to be done at the same power with about half as many subjects

# Industry Validation of QTinno: Independent Blinded CSRC Parallel TQTS

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## Study Design

- 181 Subjects; parallel study design with time-matched baseline
- 3 replicate ECGs per subject per time point – total of 11,925 ECGs, with 11,672 ECGs included in comparative analysis (253 defective files excluded)

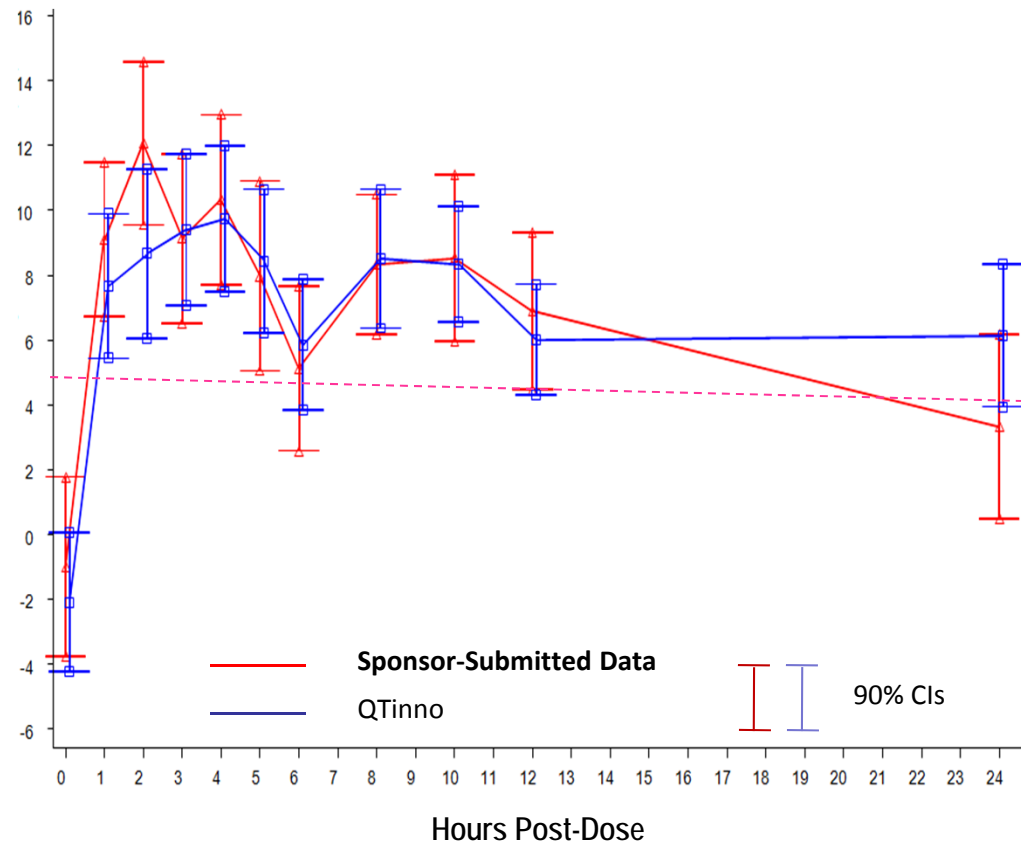
## Study conducted under strict CSRC “Rules of Engagement”\*

- CSRC provided study ECGs to NewCardio on a completely blinded basis
- All analyses of blinded QTinno measurements conducted independently by CSRC biostatisticians, without any NewCardio involvement
- “Rules of Engagement” included prior agreement that results would be made public regardless of outcome
- To date, NewCardio is the only company to accept the Rules of Engagement and complete the blinded CSRC study

\* [www.cardiac-safety.org/ecg-database/thorough-qt-datasets](http://www.cardiac-safety.org/ecg-database/thorough-qt-datasets)

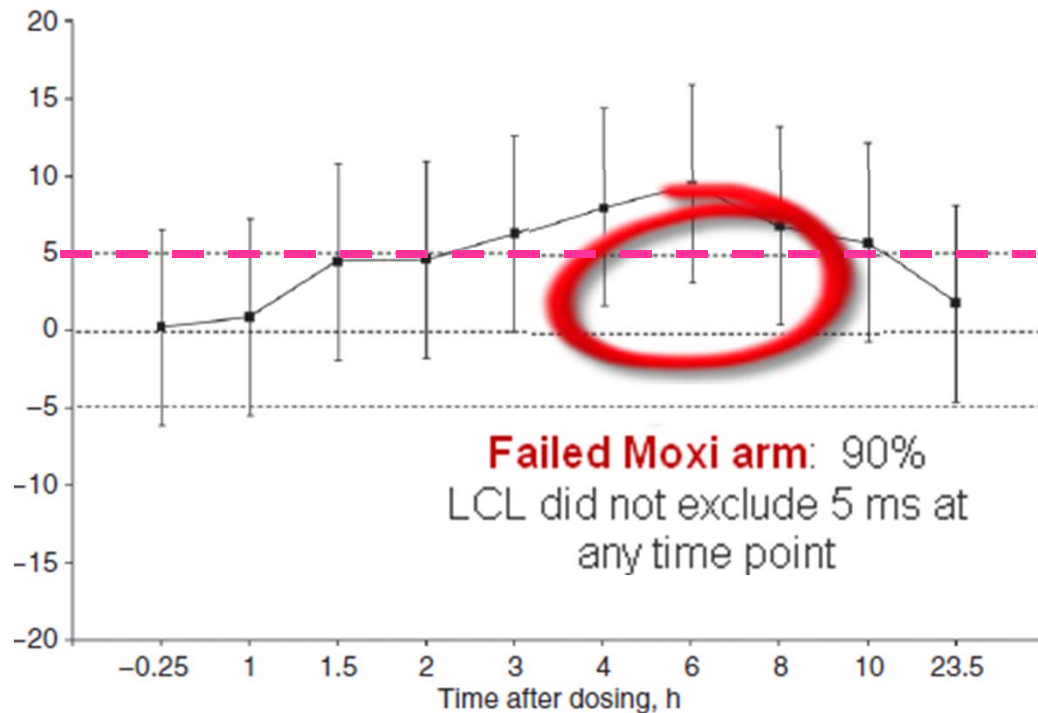
# CSRC Blinded Parallel TQTS: ddQTcF by Hour

Mean  
ddQTcF (ms)



- Both Sponsor data and QTinno show typical and valid moxi ddQTcF curve
- Both methods show 7 time points where 90% lower CI excludes 5 ms
- Less than 1.5 ms difference in point estimates at 9 of 11 time points
- For QTinno (vs Sponsor data)::
  - 90% CIs - **17% narrower**
  - Mean SD - **24% reduction**

# The Importance of Measurement Precision: A Real-World Example



Morganroth et al., *Clin Pharmacol Ther.* 2010;87(5):609

- This study failed to show assay sensitivity due to imprecision
  - Wide 90% CLs (ave  $\pm 6.3$ ms) due to very **large SD (ave  $\pm 18.5$  ms)**
  - As a result, 90% LCL fails to exclude 5 ms at any time point
- Implications of good precision
  - Less risk of a failed TQTS due to insufficient moxi effect – a failure that could easily force the Sponsor to do an entirely new TQTS
  - Less risk of a disastrous “false positive” study (i.e., drug does not prolong QT, but 90% UCL fails to exclude 10 ms)
  - Fewer subjects required for an adequately-powered study

# Improved QTc Measurements Enhance Study Power

## Factors that affect sample size

- Significance Cutoff
  - Set by FDA
- Maximum Allowable QTc Effect
  - Set by FDA
- Study Power
  - Sponsor's Discretion
- Variance of QTc
  - Subject Variability
  - Measurement Precision

Significance Cutoff      Desired Power      Std Deviation of QTc in Study Population

$$N = 2(Z_{\alpha} + Z_{\beta})^2 \times \frac{S^2}{(\mu_1 - \mu_2)^2}$$

**Number of Subjects Needed**

Max Allowable Drug Induced  $\Delta$  in Mean QTc

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# Thank You!