For 2019 ASCPT QSP Preconference

FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

# Developing and Validating an In Silico Model for Proarrhythmia Risk Assessment Under the CiPA Initiative

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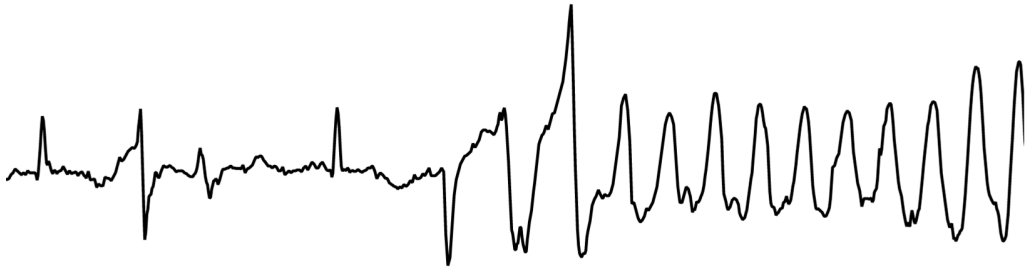
# Disclaimer

This presentation is not an official US Food and Drug Administration guidance or policy statement. No official support or endorsement by the US FDA is intended or should be inferred.

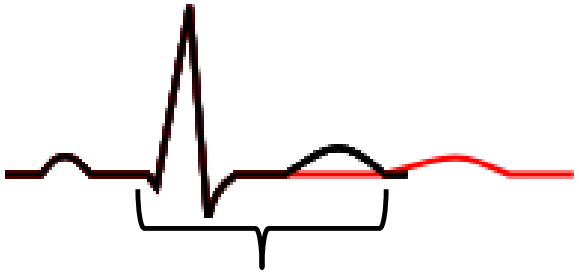
# The Regulatory Issue: Torsade de Pointes

Torsade de pointes …



↓

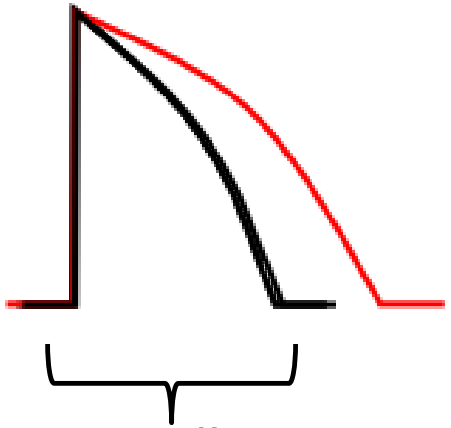
Is associated with QT prolongation …



QT interval

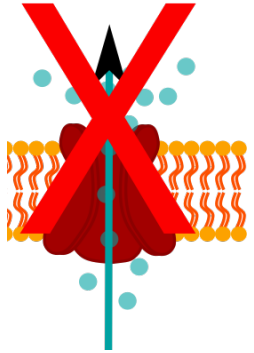
↓

Is associated with action potential prolongation …



Heart cell action potential duration

Is associated with hERG channel block →



Potassium ions

# Current Regulatory Guidelines

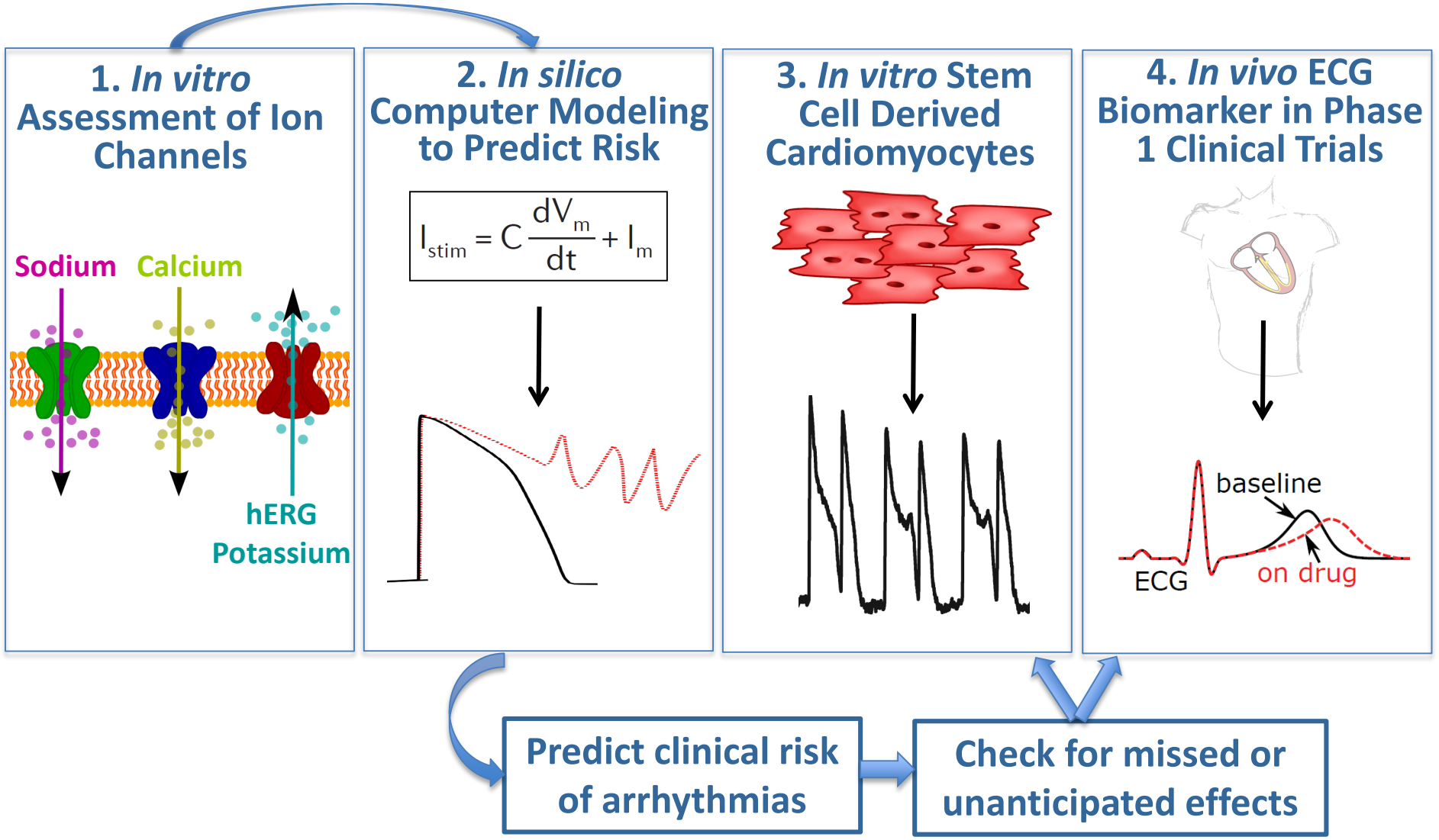
- S7B: Non-clinical cardiac safety pharmacology
  - hERG potassium channel block
  - Non-clinical action potential or QT study

- E14: Human Clinical 'Thorough QT' study
  - Threshold of concern is ~2% increase in QT (very small!)
  - Most intensive and expensive clinical pharmacology study in drug development

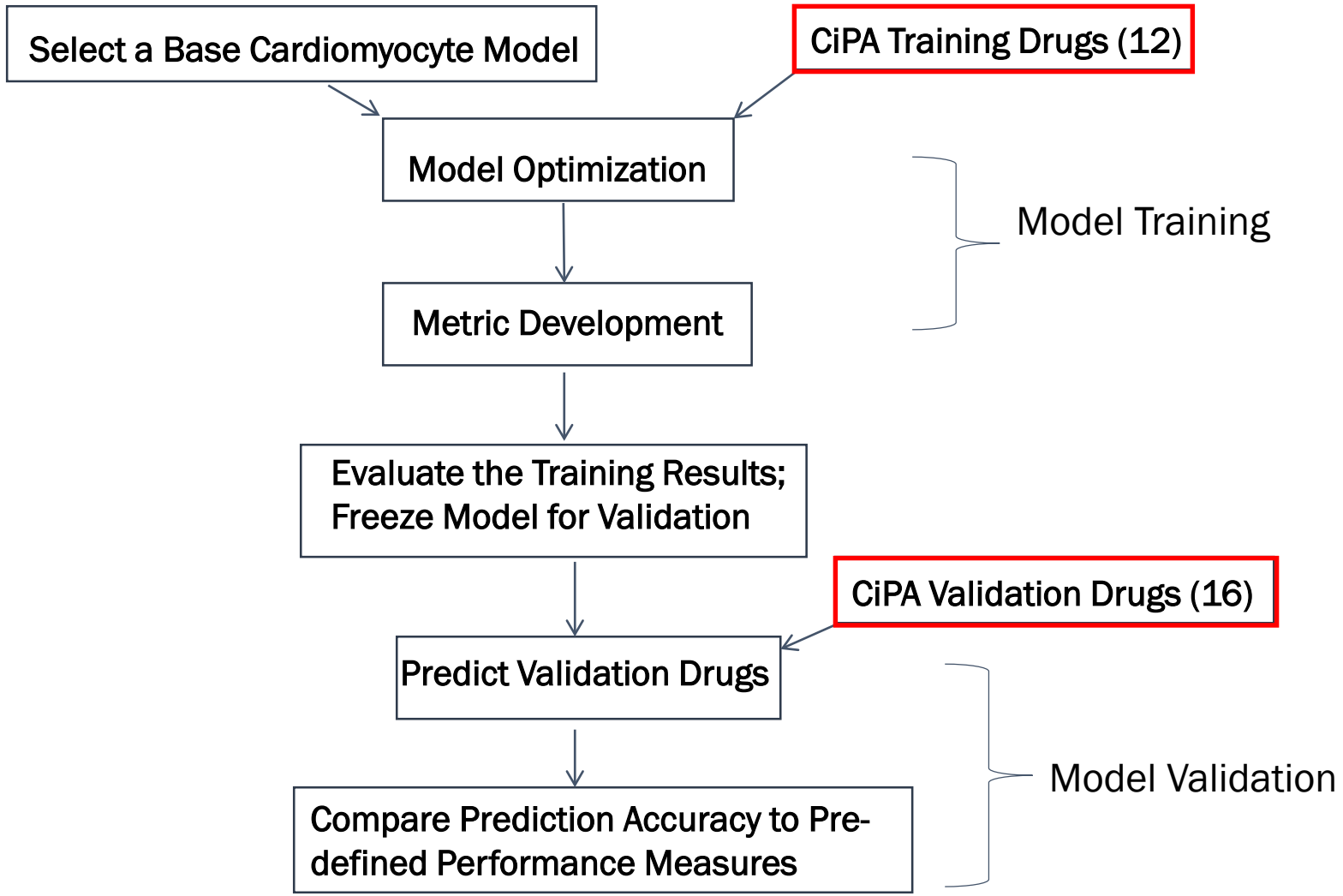
- **Primary goal is to inform whether ECG monitoring in patients is required in clinical phase 3 trials**
- **<u>Not</u> to inform whether a drug causes torsade de pointes**

**<u>As some QT prolonging drugs do not cause torsade de pointes (More mechansitic marker assessing multichannel pharmacology needed!)</u>**

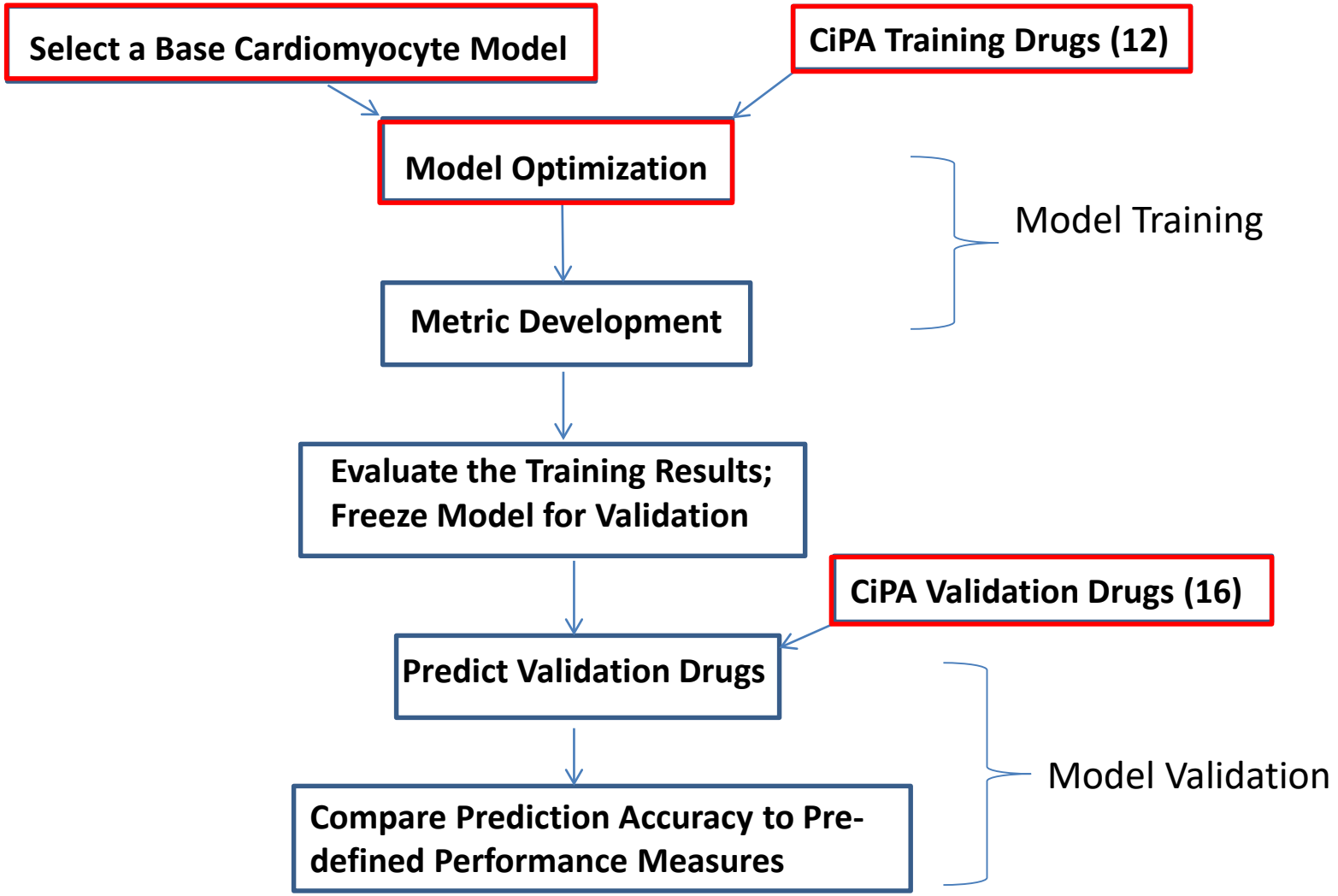
# Comprehensive *in vitro* Proarrhythmia Assay (CiPA)



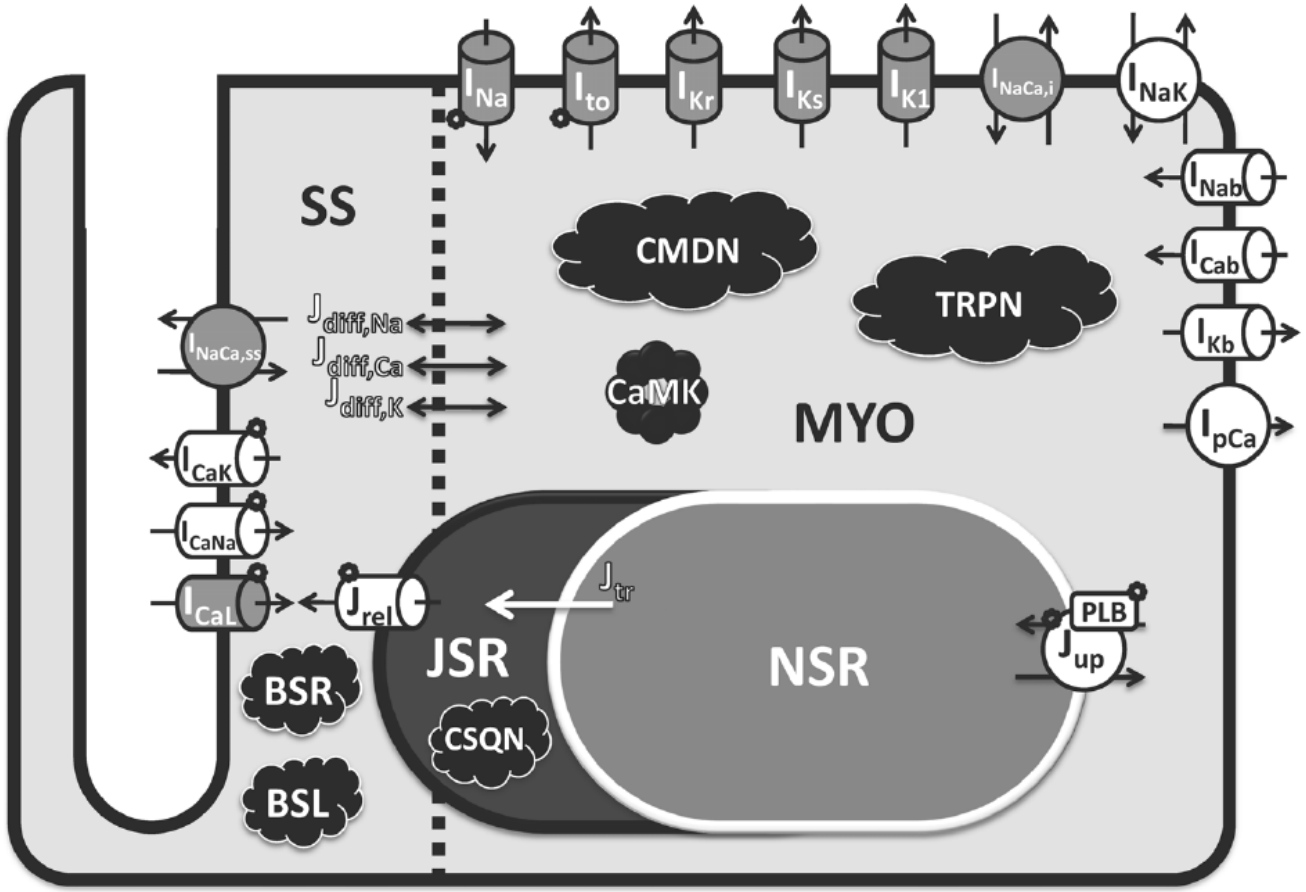
# Model Development and Validation Strategy



# Model Development and Validation Strategy



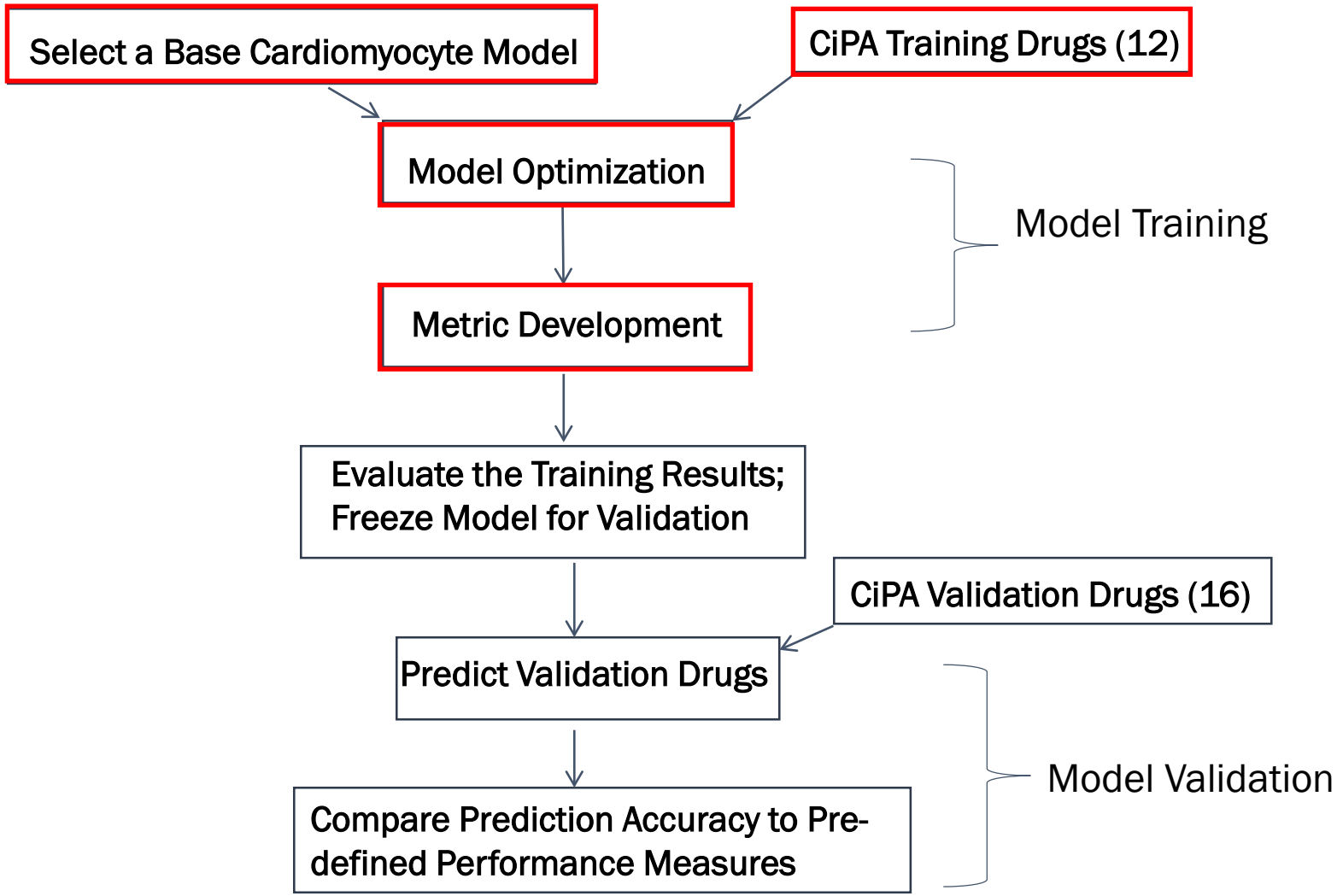
# Selecting and Improving the Base Model for CiPA



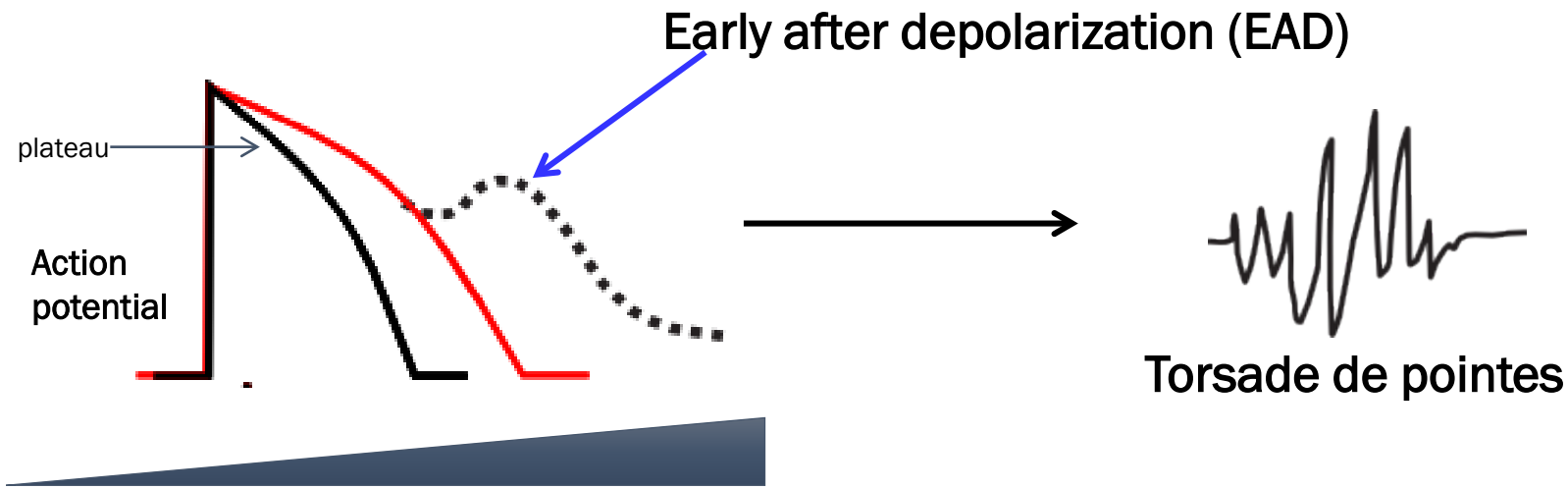

- Modeling dynamic drug-hERG interactions rather than using simple IC50s
  - Li Z et al. Circulation: Arrhythmia & Electrophysiology. 2017;10:e004628
- Optimizing model parameters so that the model can better recapitulate experimental data
  - Dutta et al. Frontiers in Physiology. 2017;8:616

O'Hara T, Virag L, Varro A, & Rudy Y (2011) *PLoS Comput Biol 7(5):e1002061.*

# Model Development and Validation Strategy



# Key Mechanism of TdP: Imbalance of Inward and Outward Currents




Increased ratio between inward and outward currents

Major currents modulating repolarization

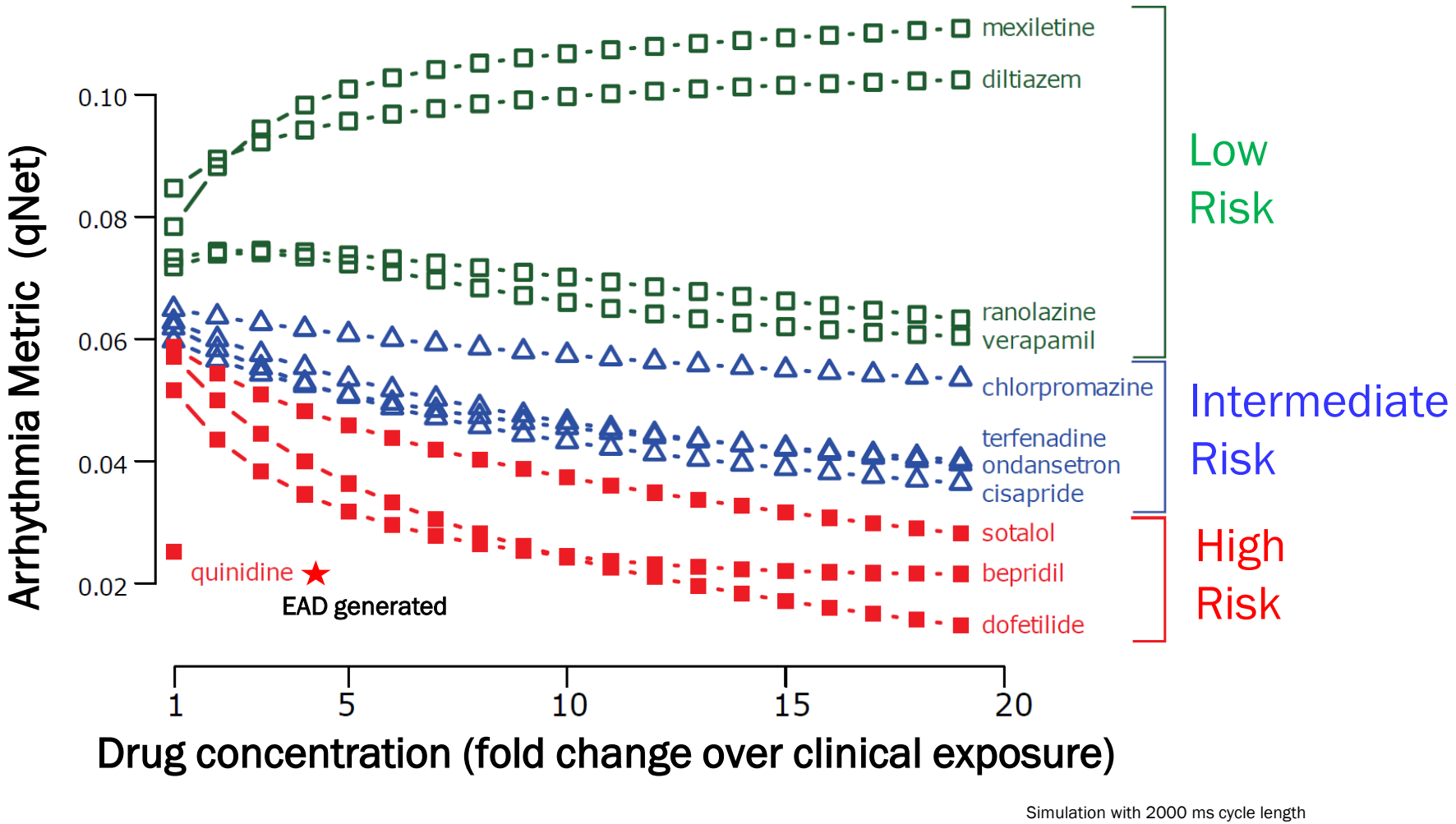
| Inward | Outward |
|---|---|
| ICaL (L type calcium) | IKr (potassium) |
| INaL (late sodium) | IKs (potassium) |
| | IK1 (potassium) |
| | Ito (potassium) |

The net current between inward and outward currents reflect their balance.

Inet = ICaL+INaL+IKr+IKs+IK1+Ito

qNet: Amount of electronic charge carried by Inet

# Performance of qNet on 12 CiPA Training Compounds




Simulation with 2000 ms cycle length

- Drug separation is good along all concentrations from 1x to 25x Cmax



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# Uncertainty Quantification for TdP Risk Assessment

frontiers in Physiology

ORIGINAL RESEARCH
published: 21 November 2017
doi: 10.3389/fphys.2017.00917

Check for updates

## Uncertainty Quantification Reveals the Importance of Data Variability and Experimental Design Considerations for *in Silico* Proarrhythmia Risk Assessment

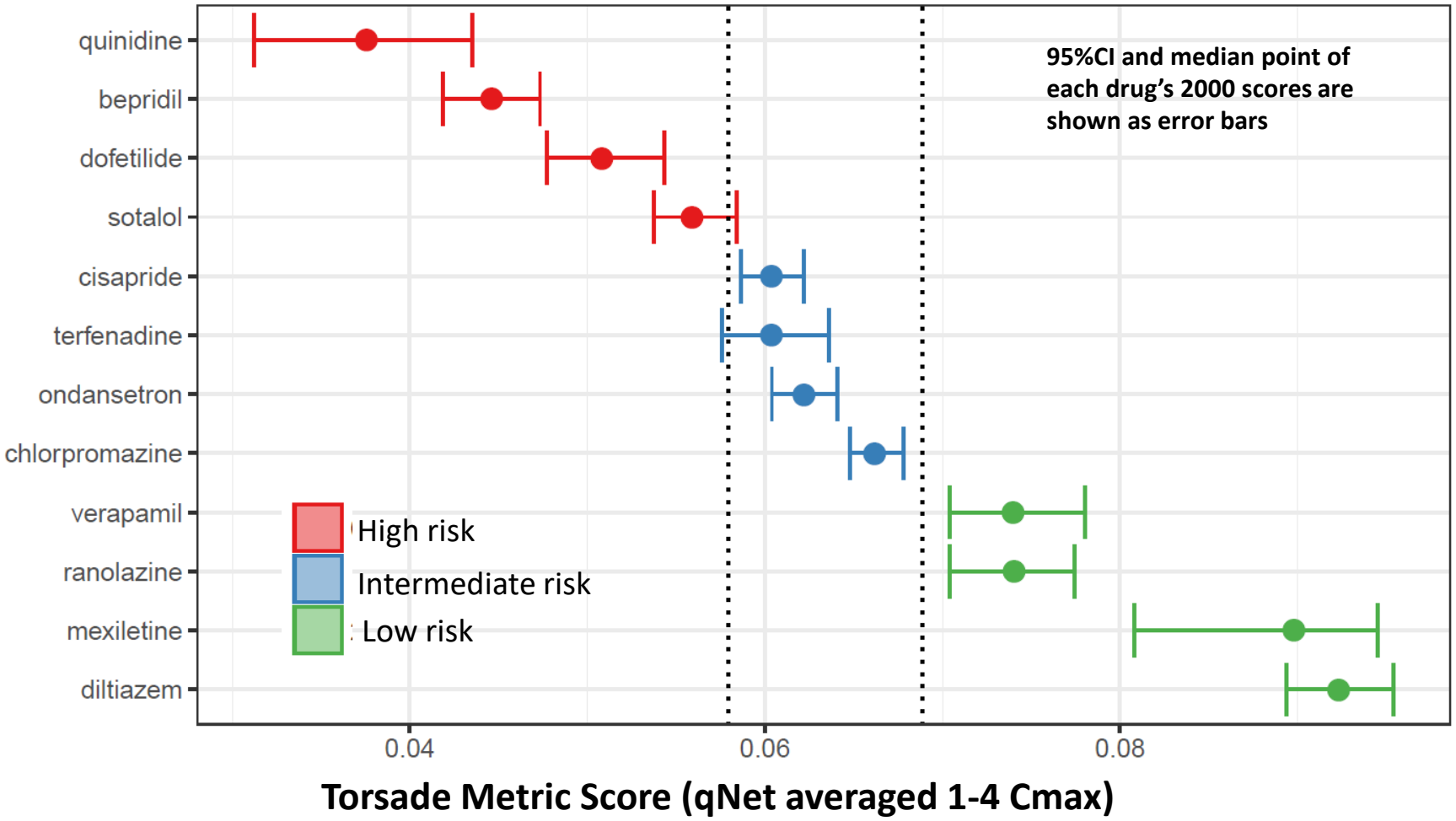
OPEN ACCESS

Edited by:

*Kelly C. Chang[1], Sara Dutta[1], Gary R. Mirams[2], Kylie A. Beattie[1], Jiansong Sheng[1], Phu N. Tran[1], Min Wu[1], Wendy W. Wu[1], Thomas Colatsky[3], David G. Strauss[1] and Zhihua Li[1]*

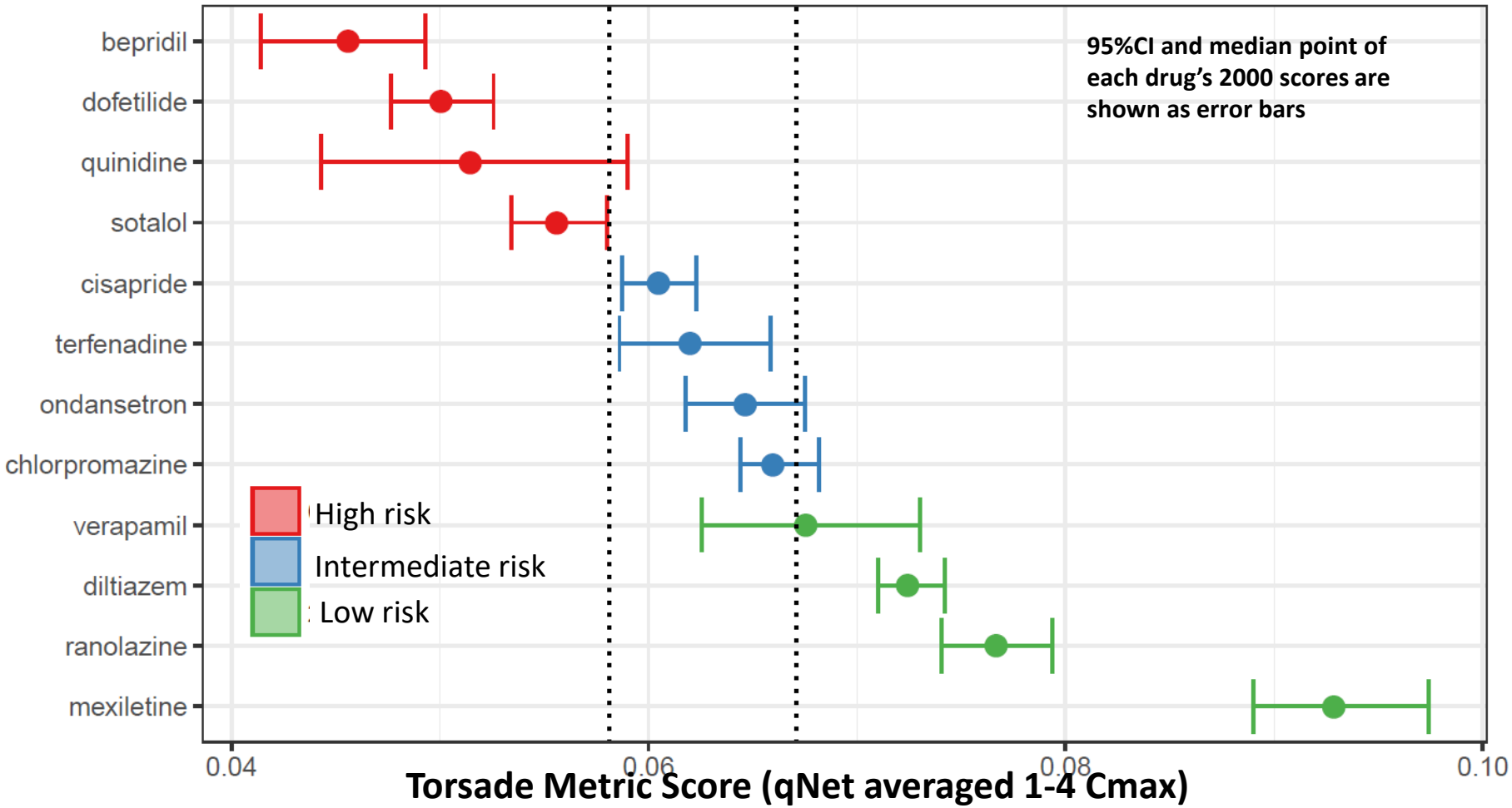
- Developed a method to translate each drug's experimental uncertainty into 2000 metric values, describing the probability distribution of its TdP risk
- Found that uncertainty is lowest when drug concentration is 1-4x Cmax

# Torsade Metric Score for Manual Training Data



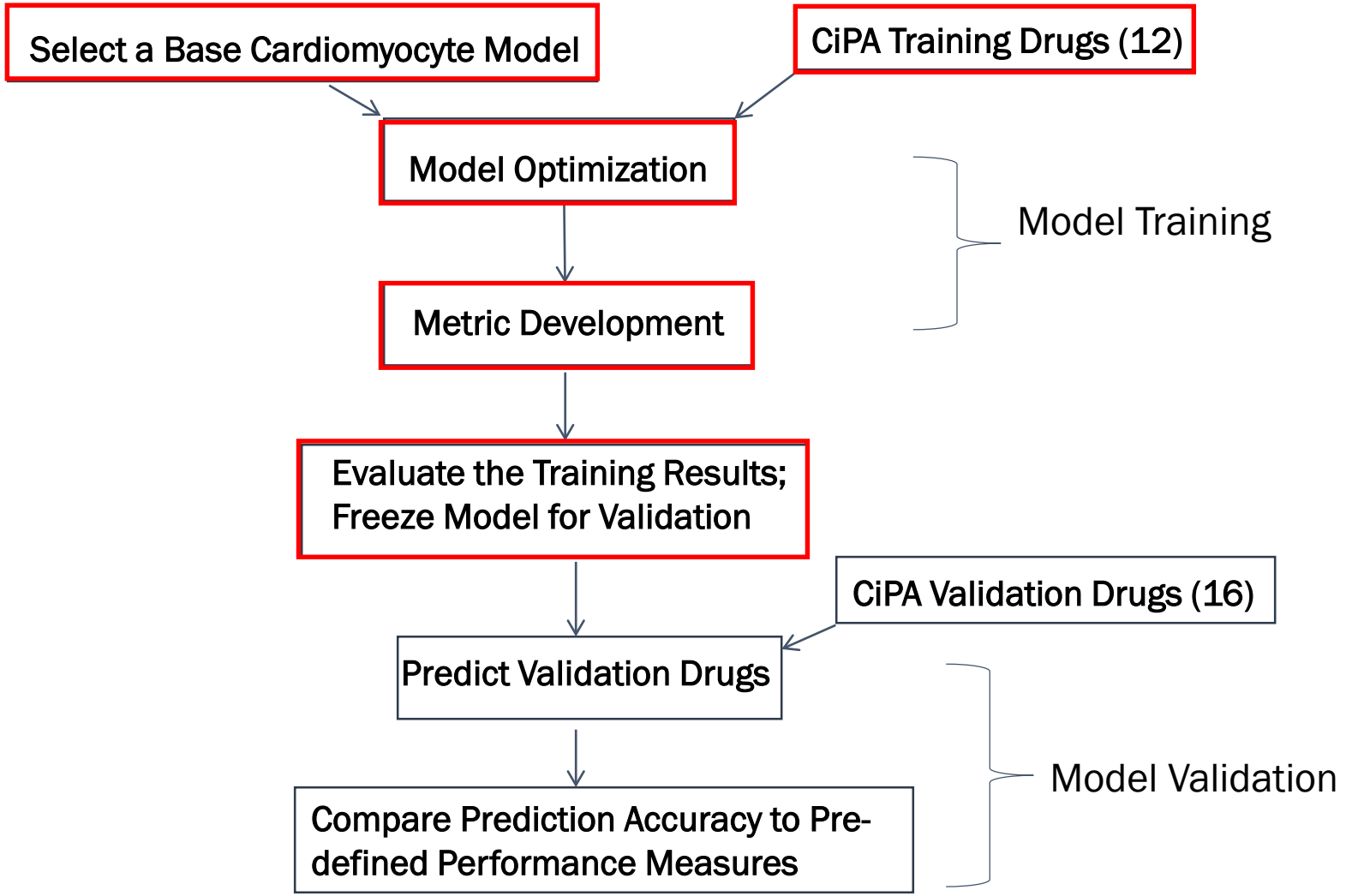

hERG (potassium channel) data: manual patch clamp
Non-hERG (sodium and calcium channel) data: manual patch clamp

# Torsade Metric Score for Hybrid Training Data




hERG (potassium channel) data: manual patch clamp
Non-hERG (sodium and calcium channel) data: automated high throughput patch clamp systems

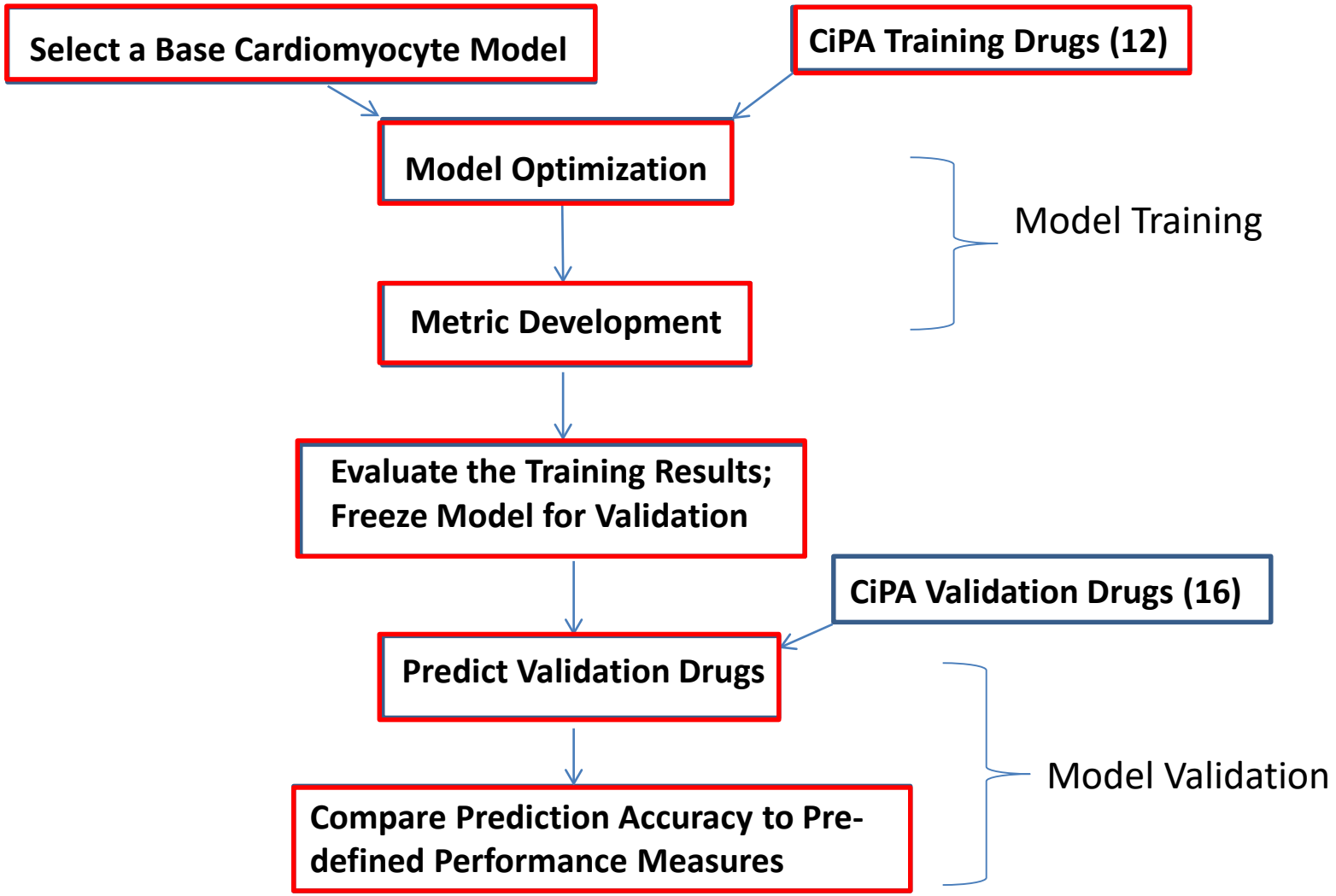
# Model Development and Validation Strategy



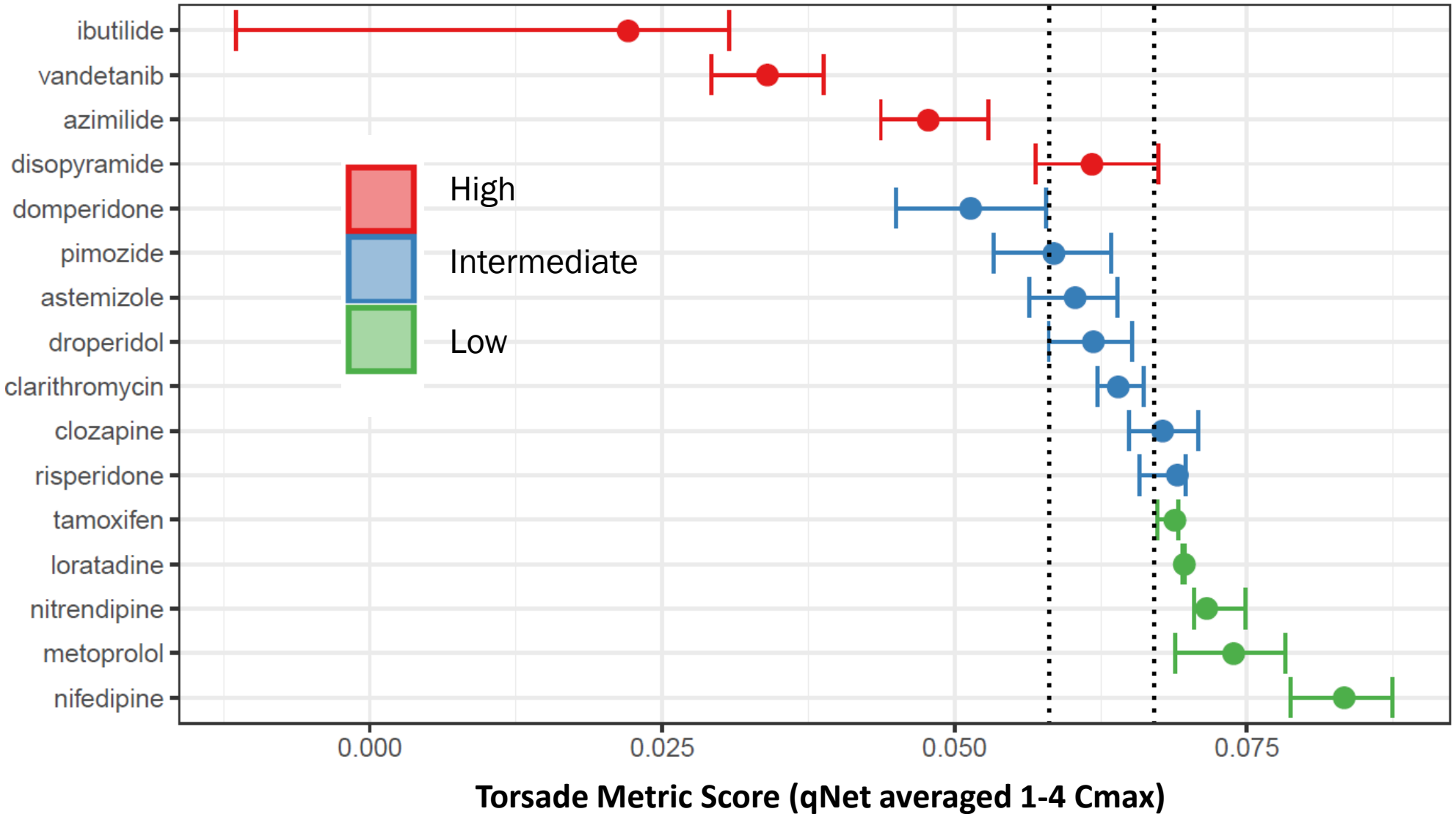
# Evaluating and Freezing Model Prior to Validation

- On March 15th 2017, FDA held a Pharmaceutical Science and Clinical Pharmacology Advisory Committee Meeting on the topic of “Model Informed Drug Development”, where CiPA was presented as a potential new regulatory paradigm to seek external expert opinions
- A Validation Procedure document was vetted by CiPA In Silico Working Group and Ion Channel Working Group, and approved by Steering Committee prior to validation
  - The published CiPAORdv1.0 model and qNet (Torsade Metric Score) metric, as well as classification thresholds, were“frozen”
  - Defined two validation datasets: one manual and one hybrid, each 16 drugs
  - Defined two types of performance measurements: ranking TdP risk without specific classification thresholds, and classifying drugs into one of the three risk categories using specific thresholds
  - For each measurements three acceptable levels: minimally acceptable, good, and excellent.

# Model Development and Validation Strategy



# Prediction of the 16 Validation Drugs (Hybrid Data)




Li Z et al. Clin Pharmacol Ther. 2018

# CiPA Progress and ICH Update

- Over two validation datasets, the CiPA model/metric generally reaches pre-defined “excellent” ranking performance (5 times excellent and 1 time good), and generally “good” to “excellent” classification performance (5 times excellent,  3 good, and 2 minimally acceptable).
- In May 2018, CiPA validation results were reported to ICH
- In Nov 2018, ICH officially formed an Implementation Working Group to incorporate CiPA-like approaches into the current S7B/E14 guidelines through Questions & Answers

(https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E14/E14S7BIWG_ConceptPaper_Final_2018_1122.pdf)

# Summary

- The CiPA model adopts the most stringent validation strategy for evaluating TdP risk prediction accuracy
- Some CiPA features could be generally applied to developing/validating/implementing QSP-type models for regulatory decision making
  - Multi-disciplinary team
  - Pre-specified development and validation strategy
  - A prospective design to strictly separate training from validation
  - Step-by-step documentation of the development and freezing of the model
  - Uncertainty quantification of the model input (pharmacological effects)
  - “Reality check” of nonclinical data and model predictions using clinical data

# Acknowledgements

**CiPA Steering Committee**

Ayako Takei, Bernard Fermini, Colette Strnadova, David Strauss, Derek Leishman, Gary Gintant, Jean-Pierre Valentin, Jennifer Pierson, Kaori Shinagawa, Krishna Prasad, Kyle Kolaja, Natalia Trayanova, Norman Stockbridge, Philip Sager, Tom Colatsky, Yasunari Kanda, Yuko Sekino, Zhihua Li

**All CiPA Working groups**

- Ion Channel working group
- In silico working group
- Cardiomyocyte working group
- Phase 1 ECG working group

**ALL** contributors to CiPA (**there are a lot!**)

- HESI, SPS, CSRC
- FDA, EMA, PMDA, NIHS, Health Canada
- **Many** pharmaceutical and laboratory device companies
- Academic collaborators

**FDA Contributors**

- Norman Stockbridge
- Christine Garnett
- John Koerner
- Issam Zineh

Ion channel

- Wendy Wu
- Phu Tran
- Jiansong Sheng
- Min Wu
- Aaron Randolph

In silico

- Zhihua Li
- Sara Dutta
- Kelly Chang
- Kylie Beattie
- Xiaomei Han
- Bradley Ridder

Cardiomyocyte

- Ksenia Blinova
- Derek Schocken
- Li Pang

Phase 1 ECG biomarker

- Jose Vicente
- Lars Johannesen
- Meisam Hosseini
- Robbert Zusterzeel
- Murali Matta
- Roberto Ochoa-Jimenez

# BACKUP

# Ranking Performance

| Performance Measure | Interpretation | Manual Dataset | Hybrid Dataset |
|---|---|---|---|
| AUC of ROC1 | Probability of ranking an Intermediate-or-High risk drug above a Low risk drug | 0.89 (0.84 – 0.95) | 0.98 (0.93 – 1) |
| AUC of ROC2 | Probability of ranking a High risk drug above an Intermediate-or-Low drug | 1 (0.92-1) | 0.94 (0.88-0.98) |
| Pairwise Ranking | Probability of correctly ranking a drug relative to CiPA reference drugs through pairwise comparison across 3 categories | 0.95 (0.92 – 0.98) | 0.96 (0.92-0.99) |

Below minimally acceptable  Minimally acceptable  Good  Excellent

For both manual and hybrid datasets, ranking performance of Torsade Metric Score all reached or are very close to excellent level.

# Classification Performance

| Performance Measure | Interpretation | Manual Dataset | Hybrid Dataset |
|---|---|---|---|
| LR+ of Threshold 1 | **How much more likely a High-or-Intermediate drug will be predicted as High-or-Intermediate, compared to a Low Risk drug?** | 4.5 (2.3 – 5) | 8e5 (7e5 – 1e6) |
| 1/LR- of Threshold 1 | **How much less likely a High-or-Intermediate drug will be predicted as Low Risk, compared to a Low Risk drug?** | 8.8 (4.4– 8e5) | 5.5 (3.7 – 1e6) |
| LR+ of Threshold 2 | **How much more likely a High Risk drug will be predicted as High Risk, compared to a Low-or-Intermediate Risk drug?** | 12 (4.5 – 1e6) | 6 (3 – 12) |
| 1/LR- of Threshold 2 | **How much less likely a High Risk drug will be predicted as High Risk, compared to a Low –or-Intermediate Risk drug?** | 9e5 (3.3 – 1e6) | 3.7 (3 – 9e5) |
| Mean Classification Error | Average error of classifying each of the 16 validation drugs into High, Intermediate, or Low risk category | 0.19 (0.17-0.21) | 0.25 (0.23-0.27) |

Below minimally acceptable  Minimally acceptable  Good  Excellent

For classification measures, Torsade Metric Score on the manual and hybrid datasets mostly hit good to excellent performance.