For 2019 CPATH Biomarkers Program Workshop

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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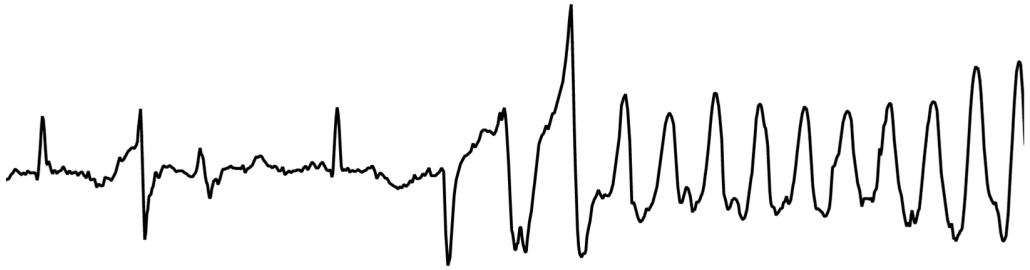
Disclaimer

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.

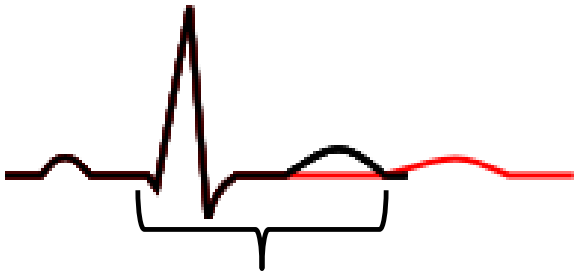
The Regulatory Issue: Torsade de Pointes

Torsade de pointes …



↓

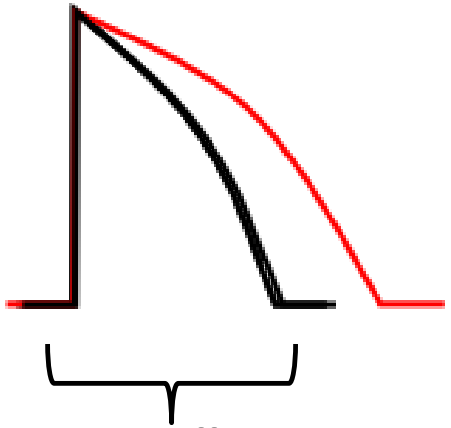
Is associated with QT prolongation …



QT interval

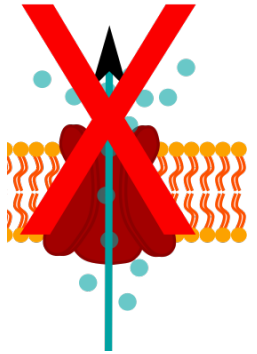
↓

Is associated with action potential prolongation …



Heart cell action potential duration

Is associated with hERG channel block →



Potassium ions

Current Regulatory Guidelines

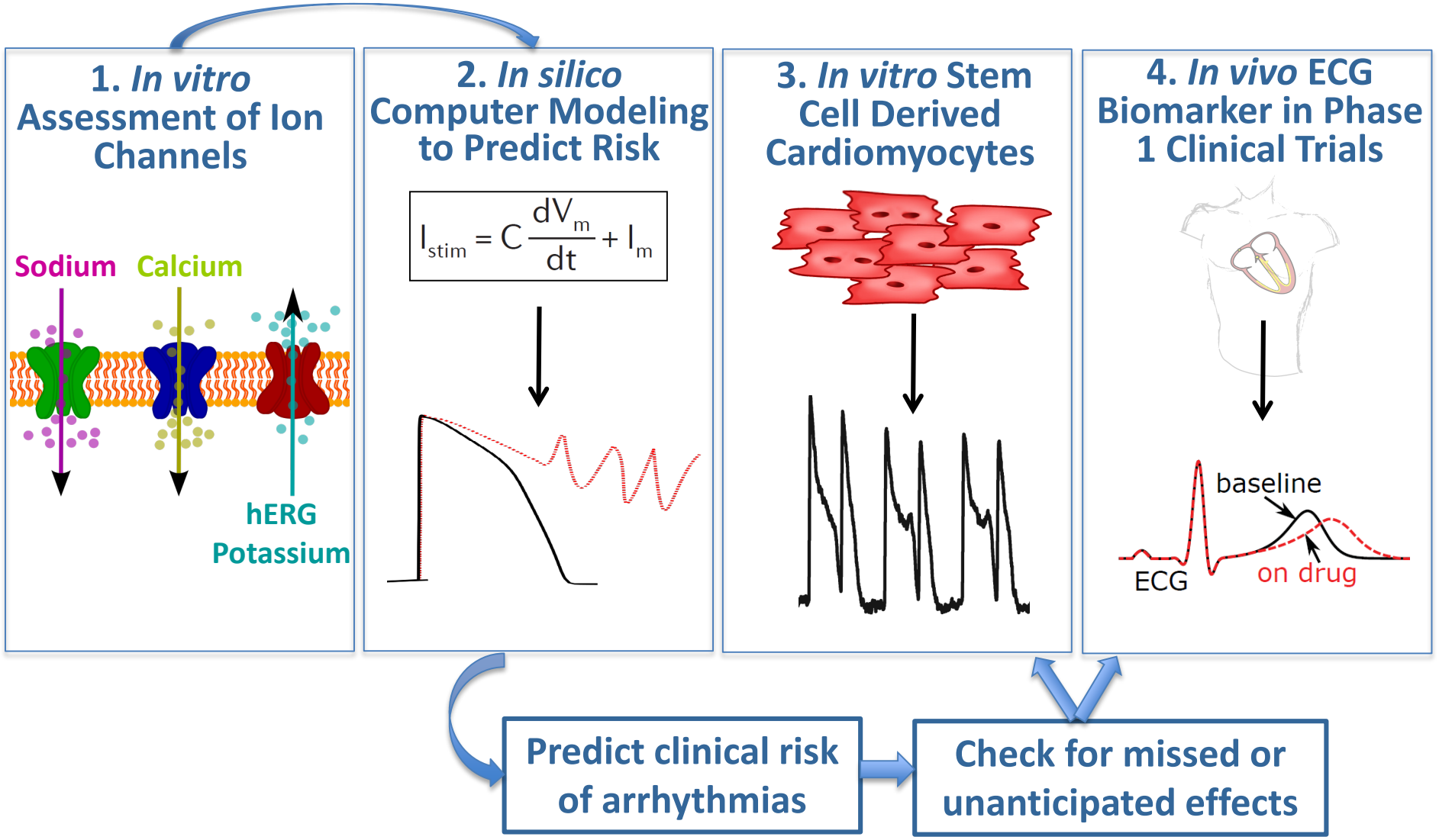
- S7B: Non-clinical cardiac safety pharmacology
  - hERG potassium channel block
  - Non-clinical action potential or QT study

- 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

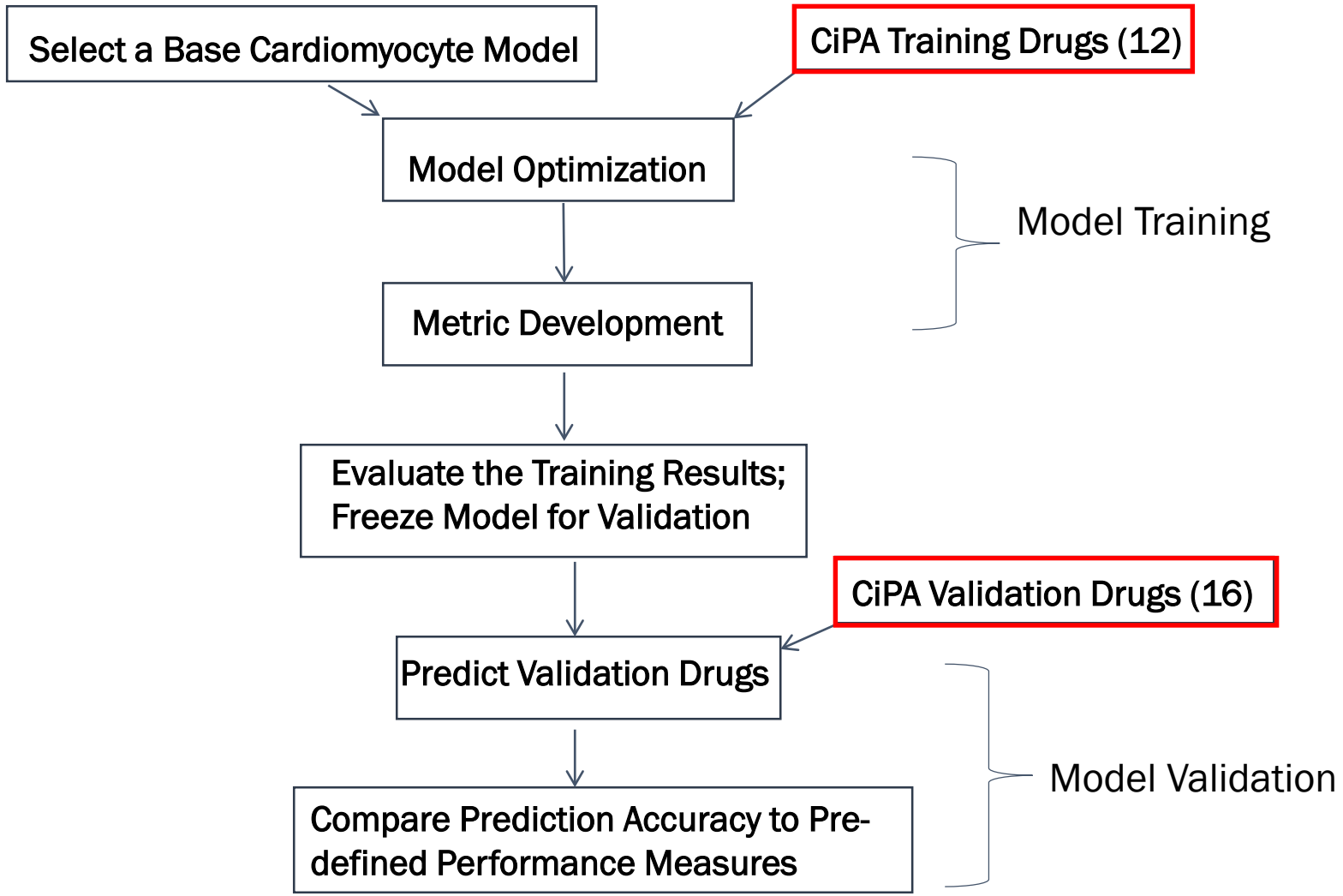
- **Primary goal is to inform whether ECG monitoring in patients is required in clinical phase 3 trials**
- **<u>Not</u> to inform whether a drug causes torsade de pointes**

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

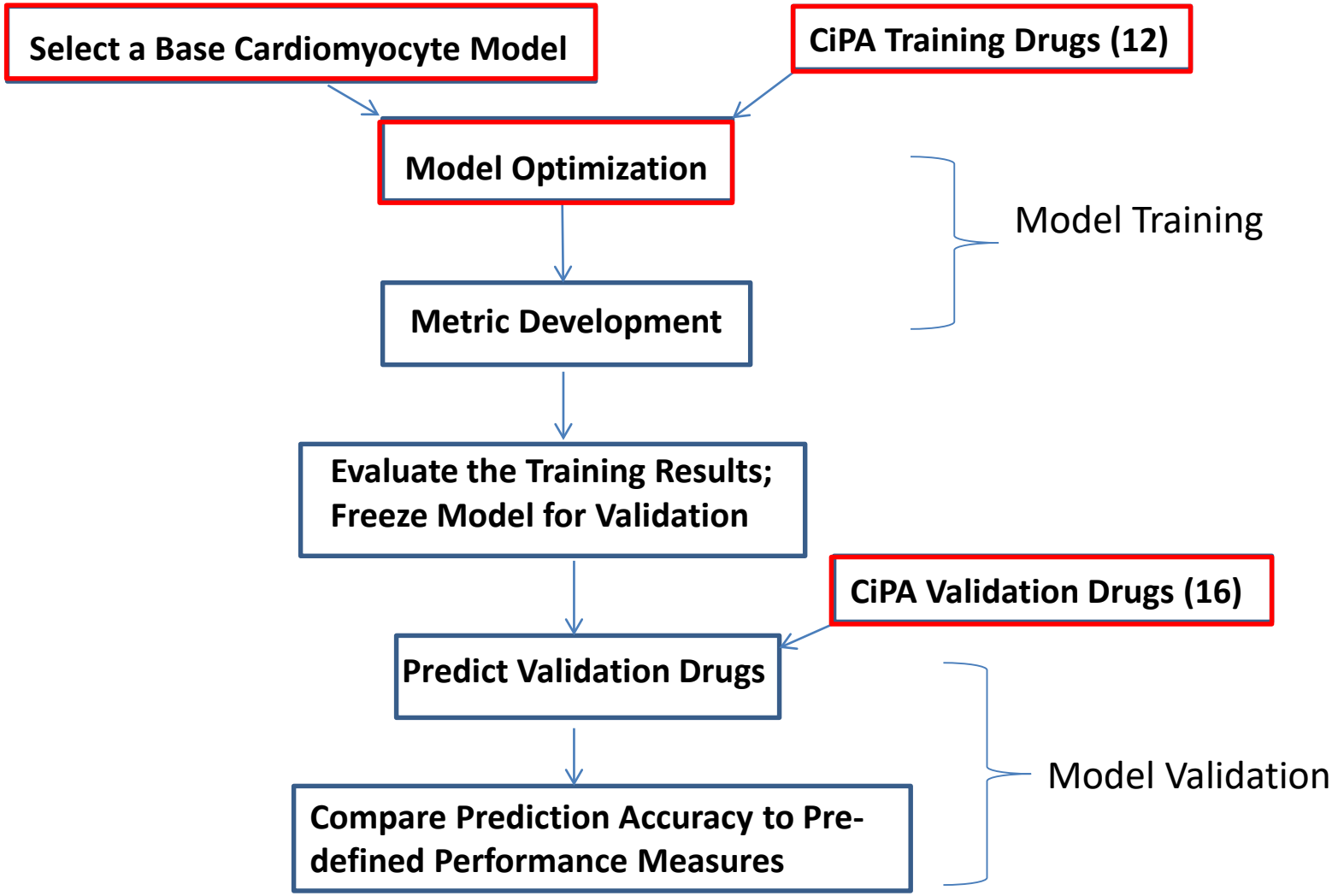
Comprehensive *in vitro* Proarrhythmia Assay (CiPA)



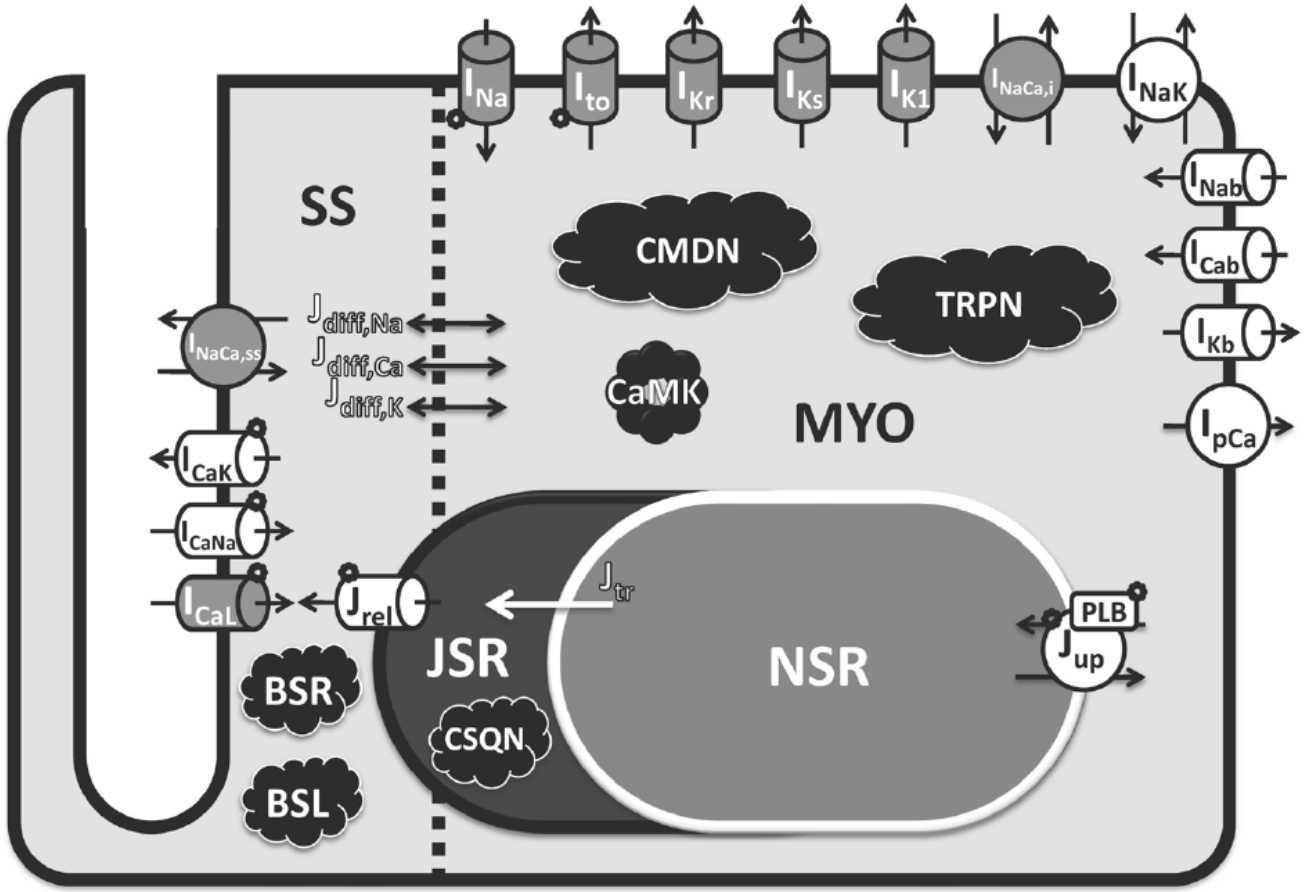
Model Development and Validation Strategy



Model Development and Validation Strategy



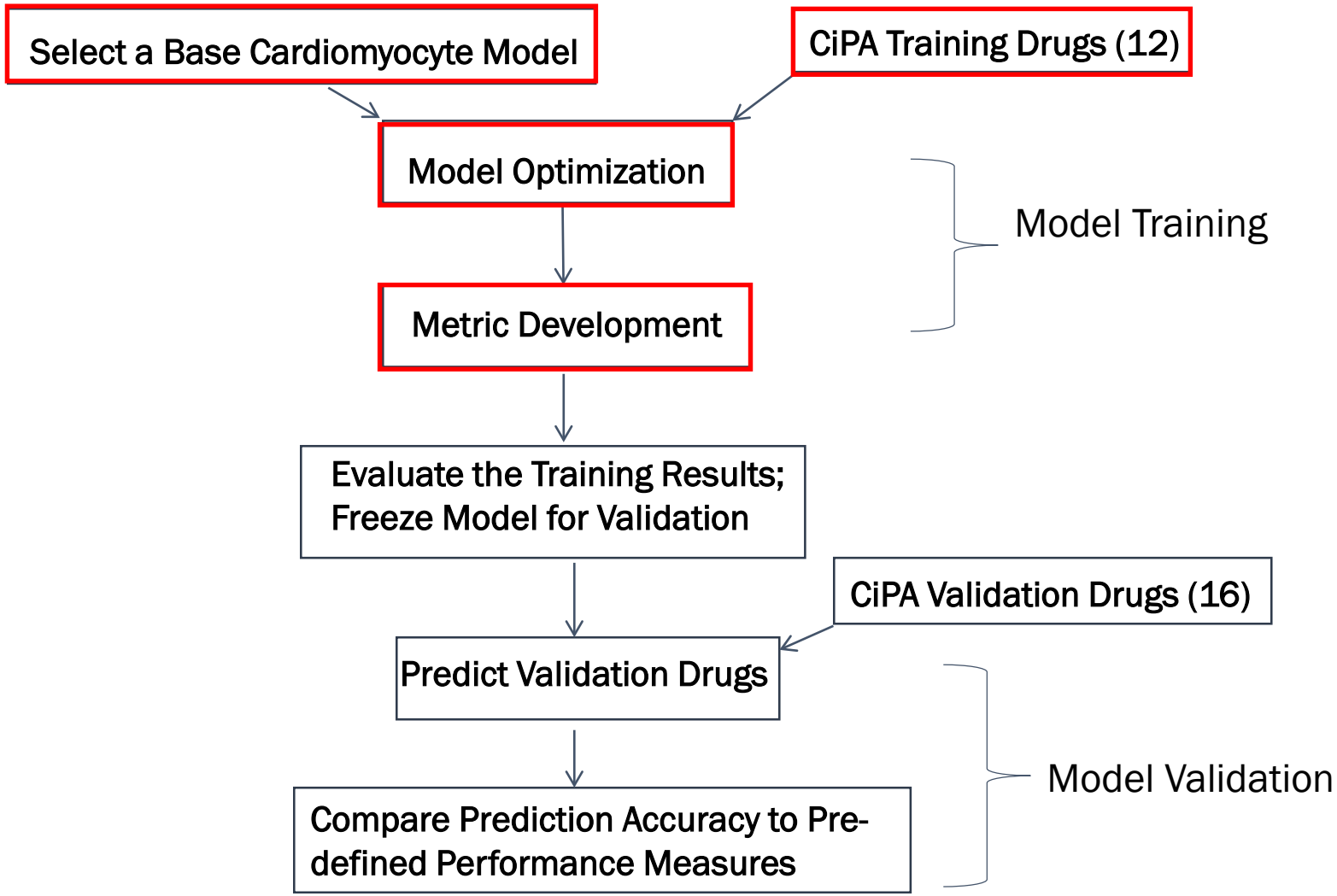
Selecting and Improving the Base Model for CiPA



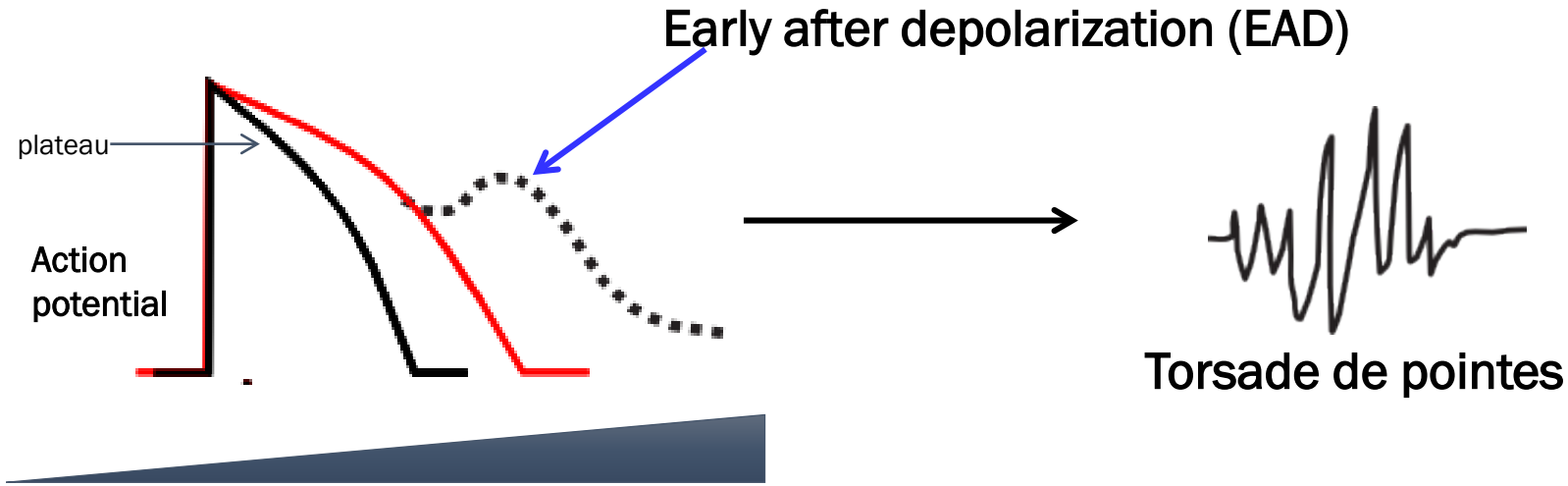
O'Hara T, Virag L, Varro A, & Rudy Y (2011) *PLoS Comput Biol 7(5):e1002061.*

- 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
- Developing a statistical framework to translate experimental variability into prediction uncertainty
  - Kelly et al. Frontiers in Physiology. 2017;8:917

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

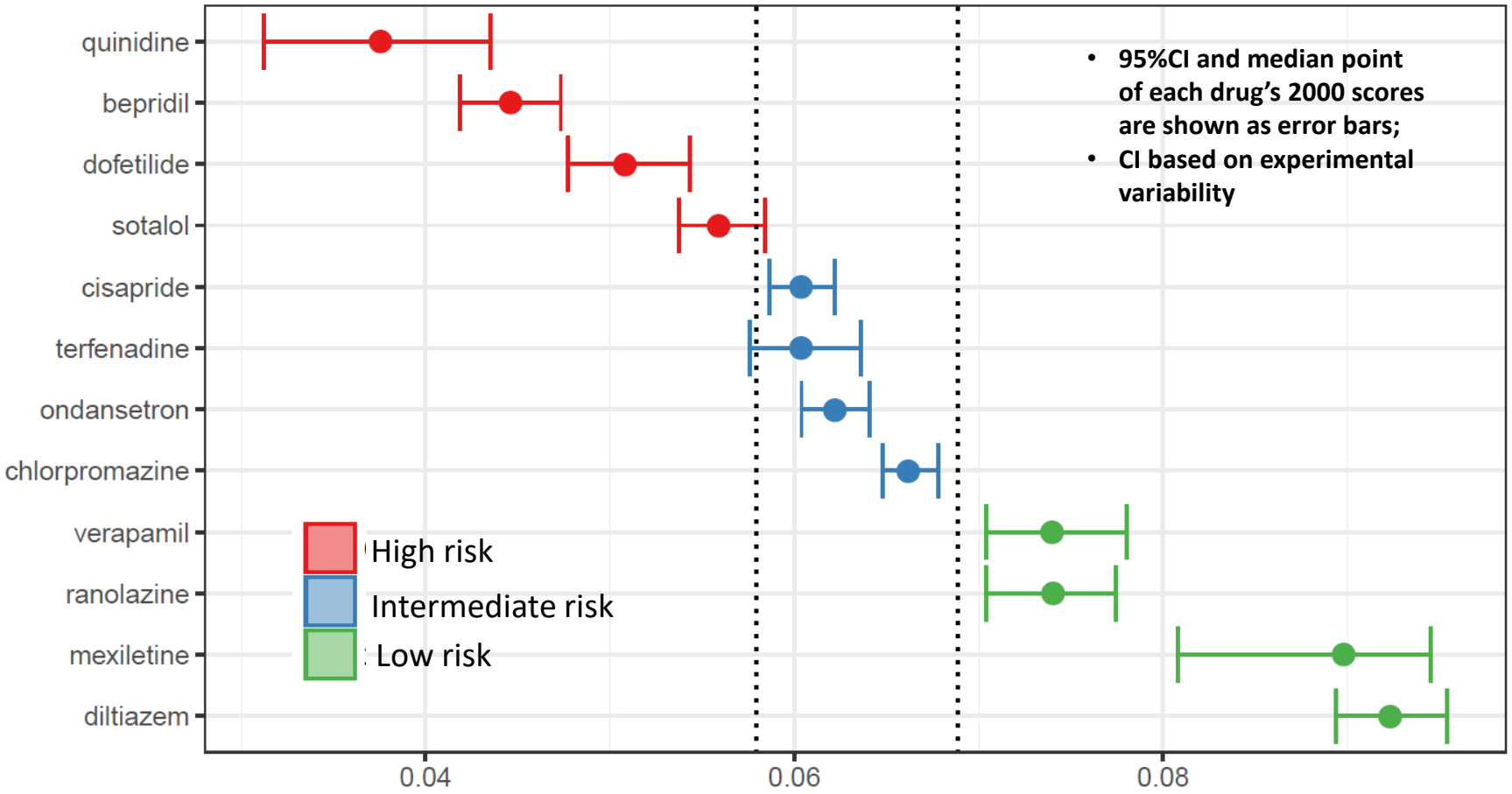
Inward	Outward
ICaL (L type calcium)	IKr (potassium)
INaL (late sodium)	IKs (potassium)
	IK1 (potassium)
	Ito (potassium)

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

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

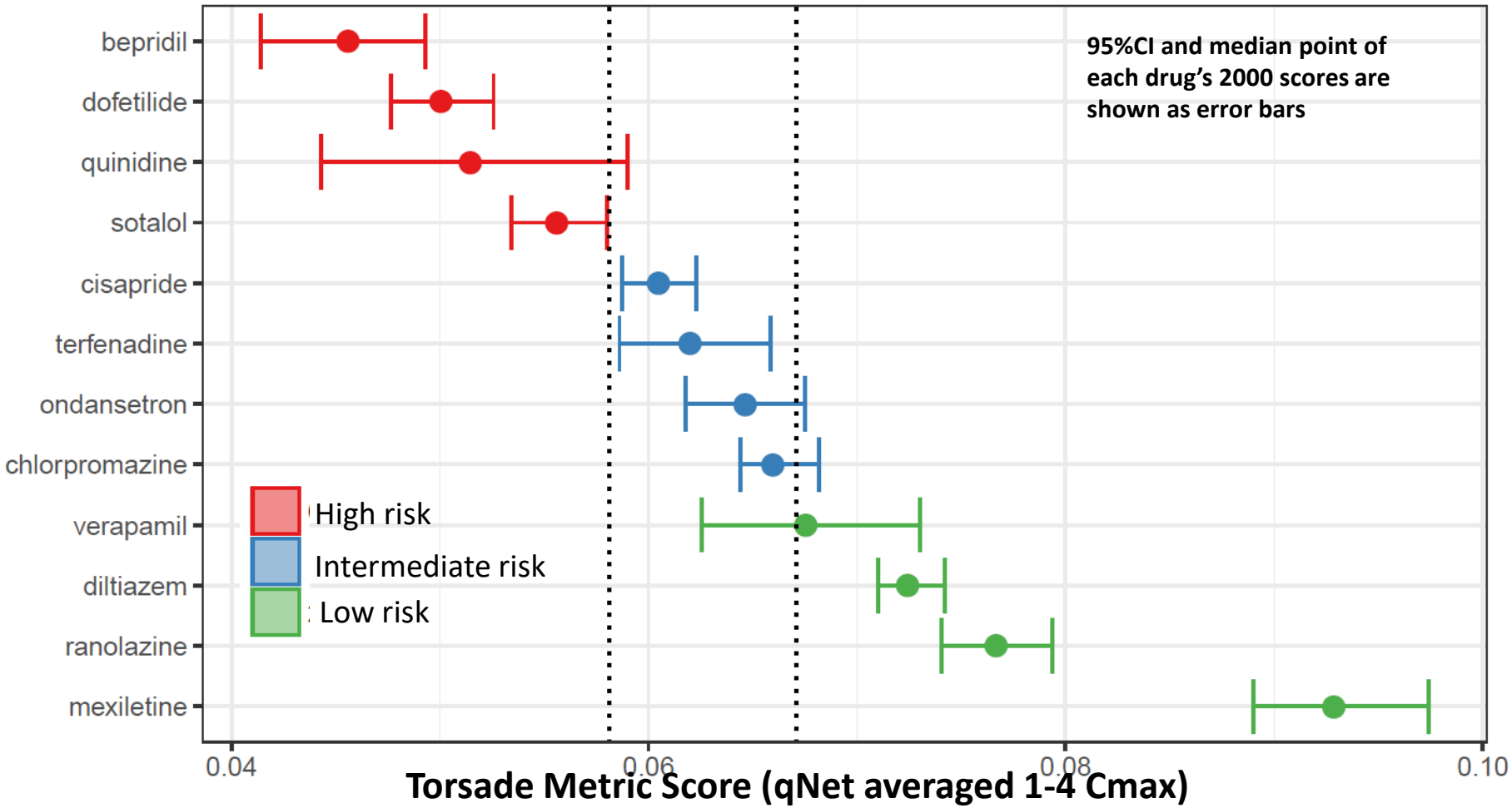
qNet: Amount of electronic charge carried by Inet

Torsade Metric Score for Manual Training Data



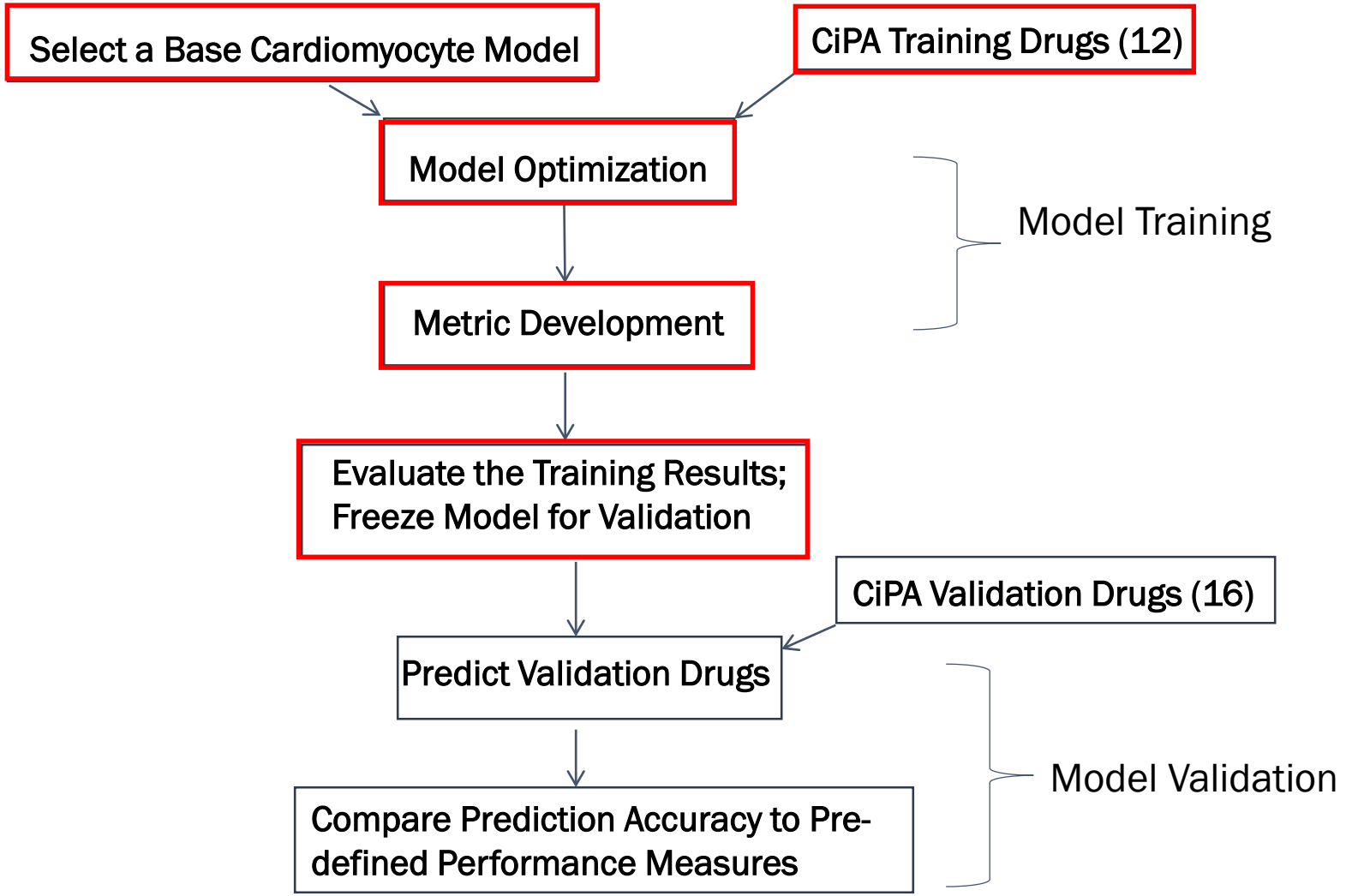
hERG (potassium channel) data: manual patch clamp
Non-hERG (sodium and calcium channel) data: manual patch clamp

Torsade Metric Score for Hybrid Training Data

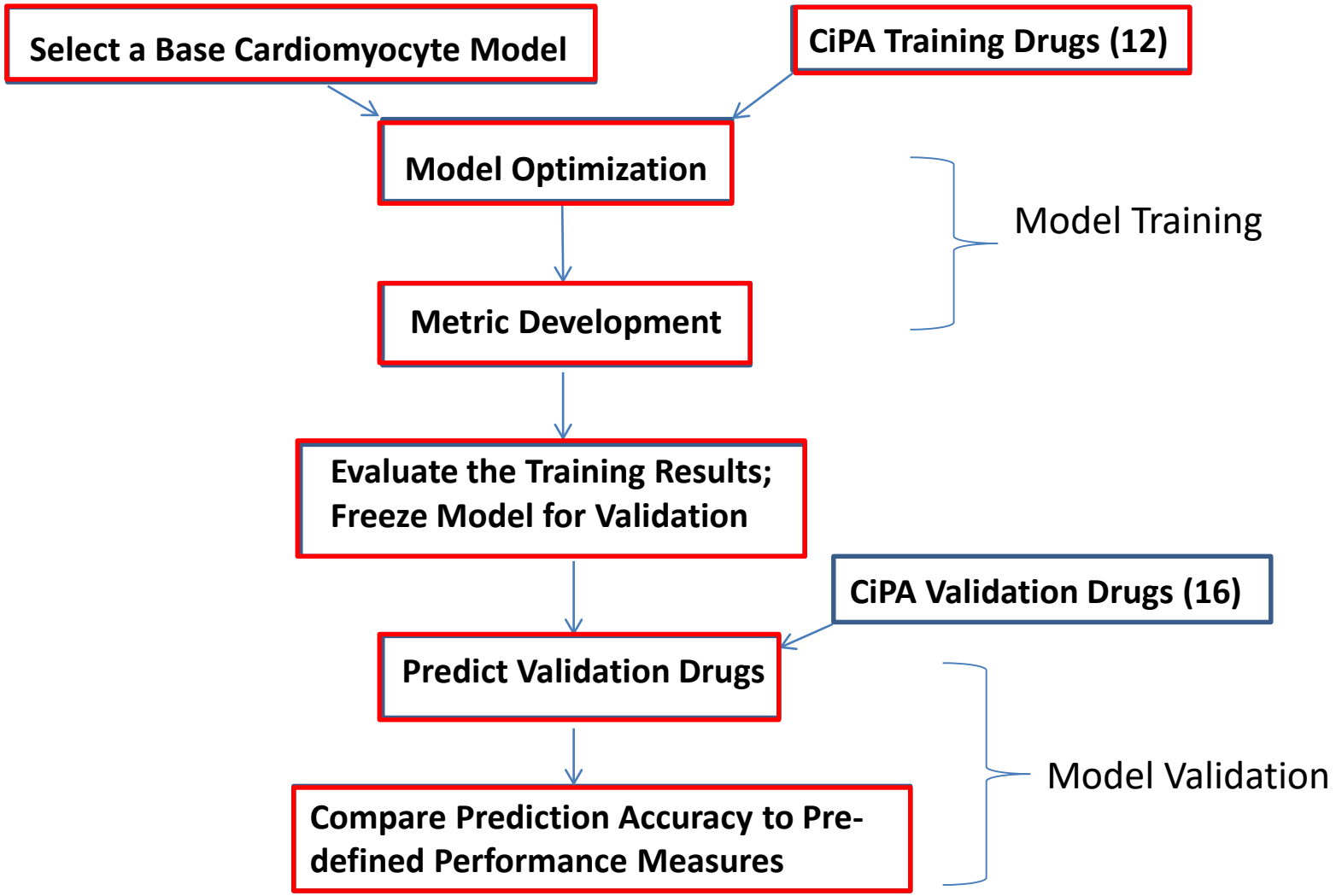


hERG (potassium channel) data: manual patch clamp
Non-hERG (sodium and calcium channel) data: automated high throughput patch clamp systems

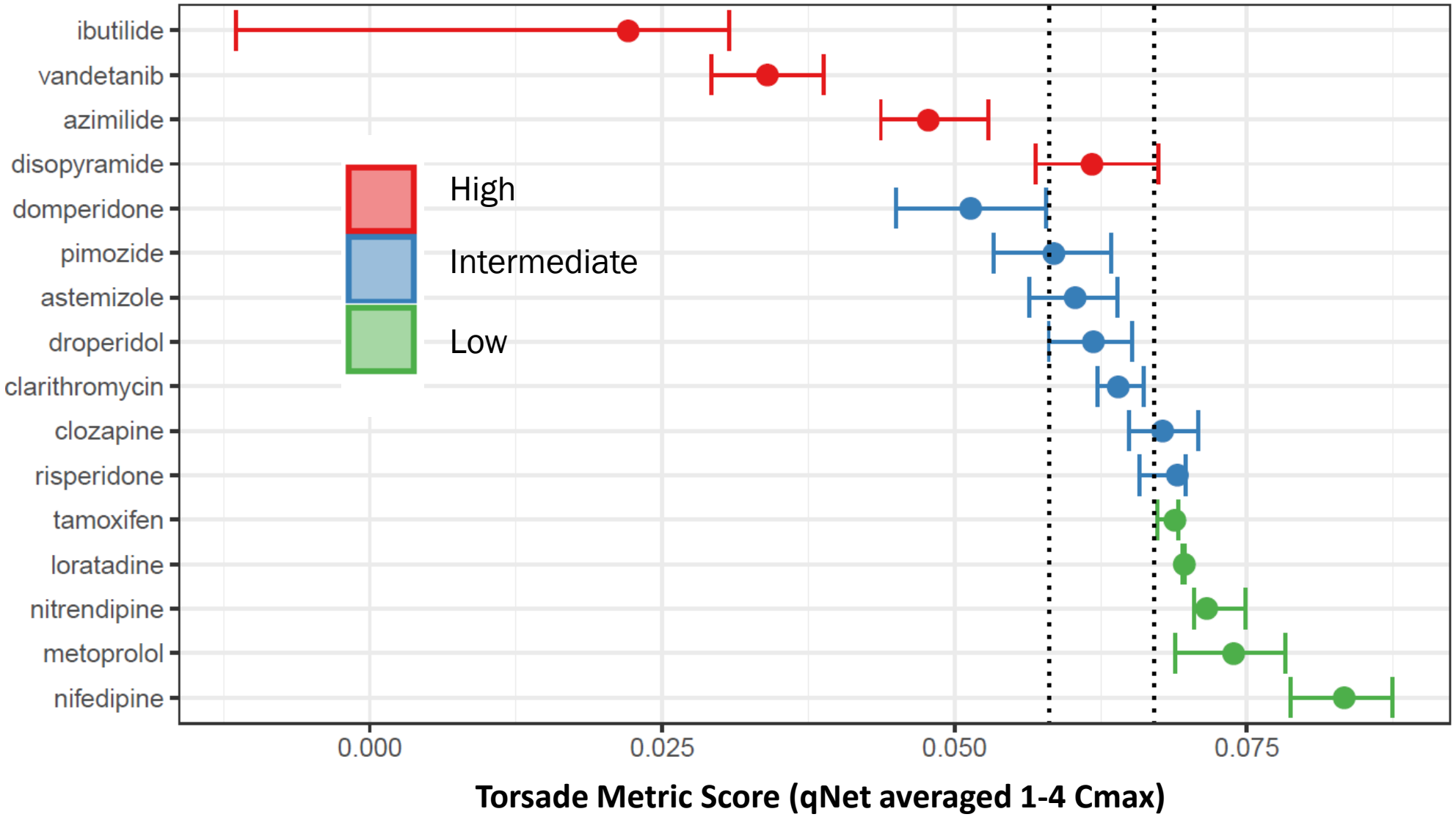
Model Development and Validation Strategy



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)

Implications

- Six general principles as learned from the CiPA development process
  - A defined endpoint consistent with the context of use
  - Fully disclosed risk scoring algorithm allowing users to reproduce the model development process
  - A defined set of experimental protocols and covered mechanisms by the model (domain of applicability)
  - A prespecified analysis plan and qualification criteria, separating training from validation
  - A mechanistic interpretation of the model and metric
  - Uncertainty quantification of the model input (pharmacological effects)
- Principles will be published as a consensus white paper co-authored by a large group of experts in the field
- Being discussed by ICH and FDA as general guidelines to evaluate regulatory acceptability of any (computational or experimental) models/biomarkers to evaluate proarrhythmia risk

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.