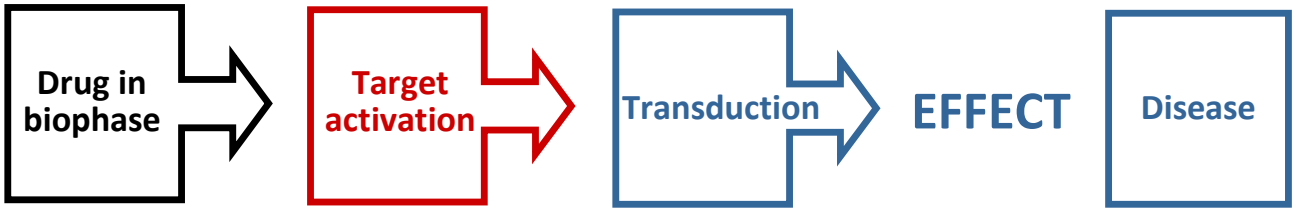

Collaborative data resources
TIPharma PKPD modeling platform

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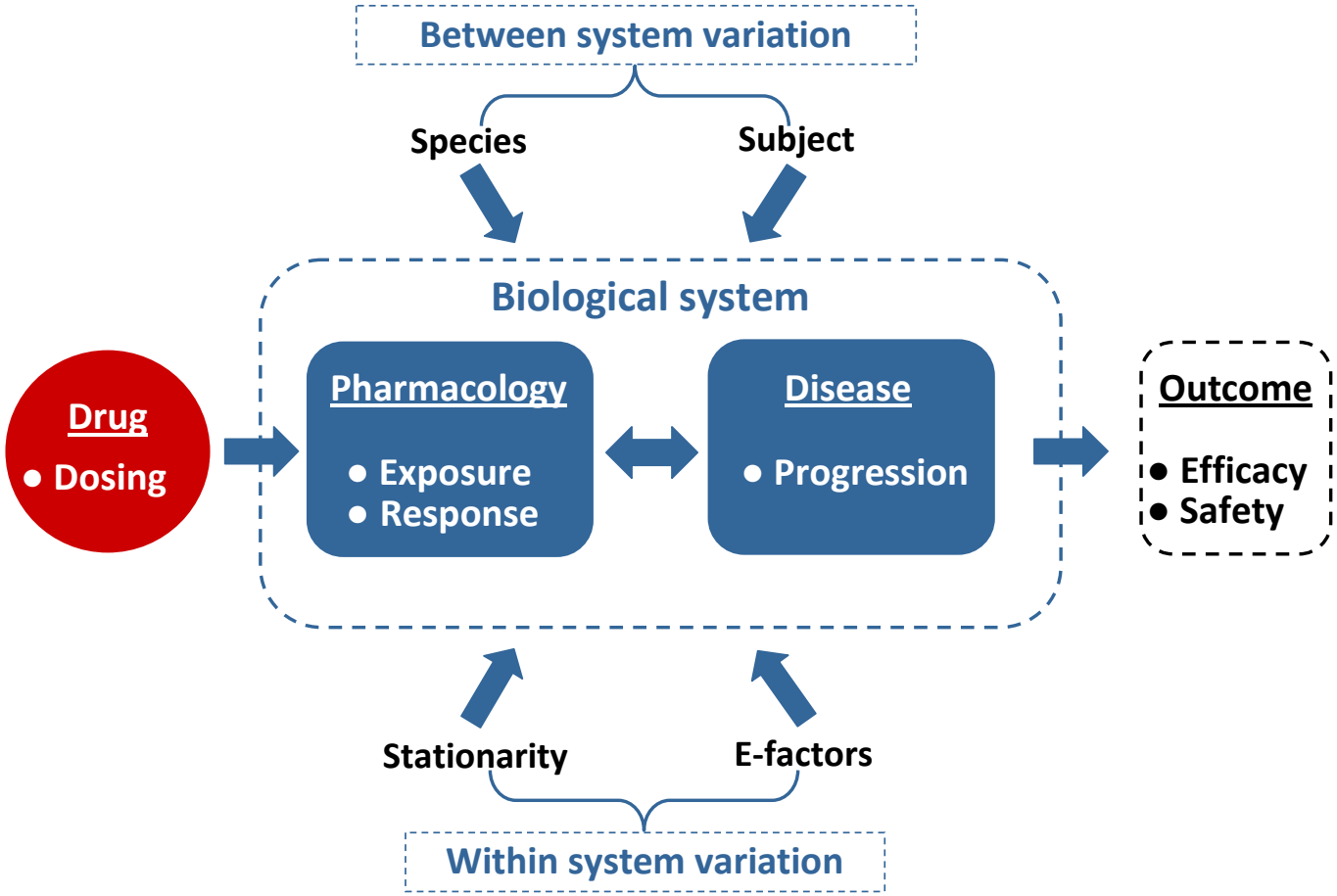
EFPIA/EMA Workshop 01 December 2010

Leiden/Amsterdam Center for Drug Research
Leiden University/Vrije Universiteit Amsterdam

LAP&P Consultants BV
Leiden Experts on Advanced Pharmacokinetics & Pharmacodynamics

Quantitative systems pharmacology
utility of collaborative data resources



TI Pharma mechanism-based PKPD modeling platform the objective

Development and implementation of a mechanism-based PKPD modeling platform as the scientific basis for rational drug discovery and innovation

- **Mechanism-based PKPD model library**
- **Database of 'biological system specific' information**

TI Pharma mechanism-based PKPD modeling platform the organization

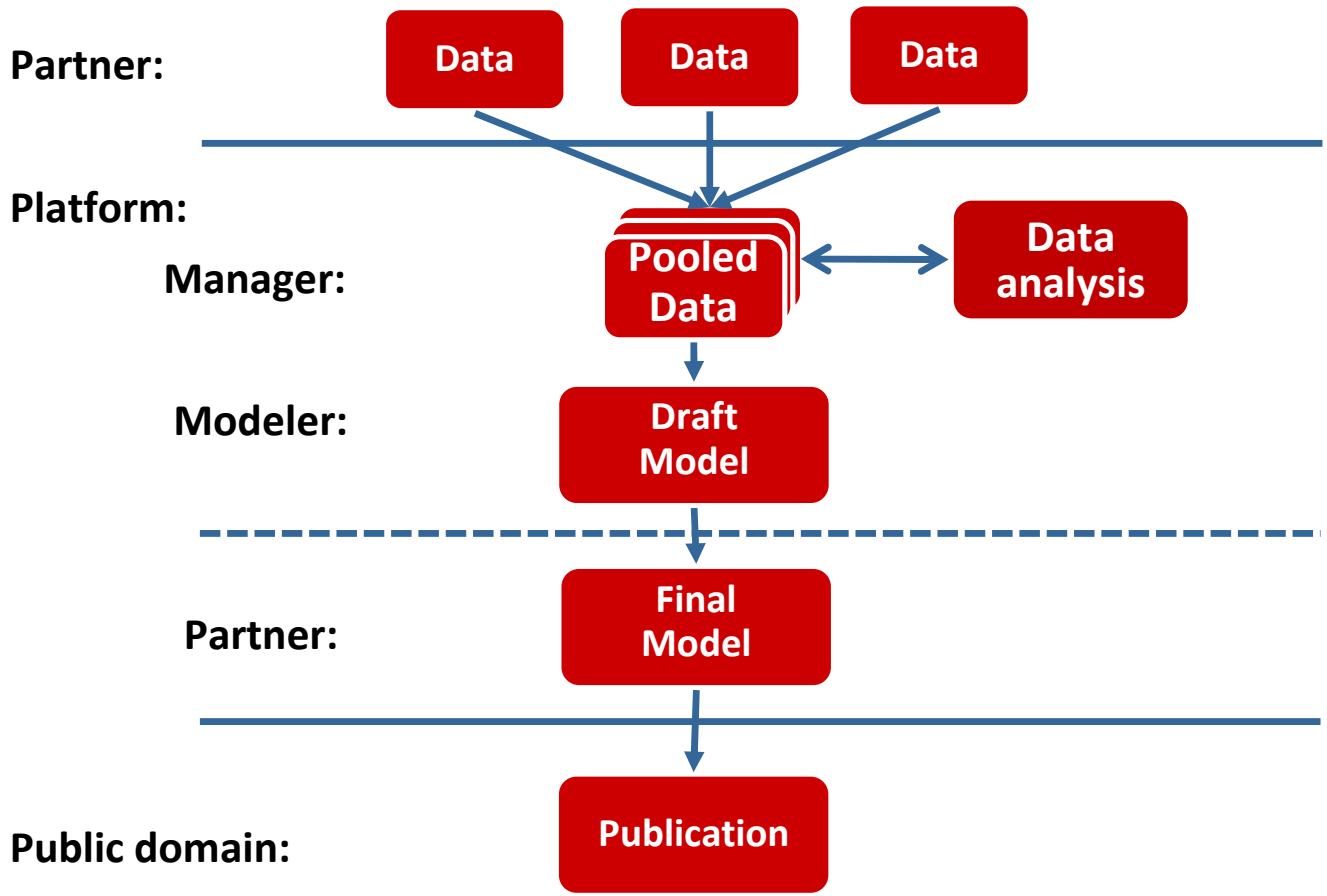
- University-industry consortium with 4 academic and 8 industrial partners
- Dedicated infrastructure for data management, data analysis and reporting: sharing of data, models and biological system specific information
- Emphasis on key factors in the discovery/development and the clinical application of novel drugs
  - Translational pharmacology (efficacy and safety)
  - Developmental pharmacology (pediatrics, elderly)
  - Disease system analysis (osteoporosis, COPD)

TI PHARMA

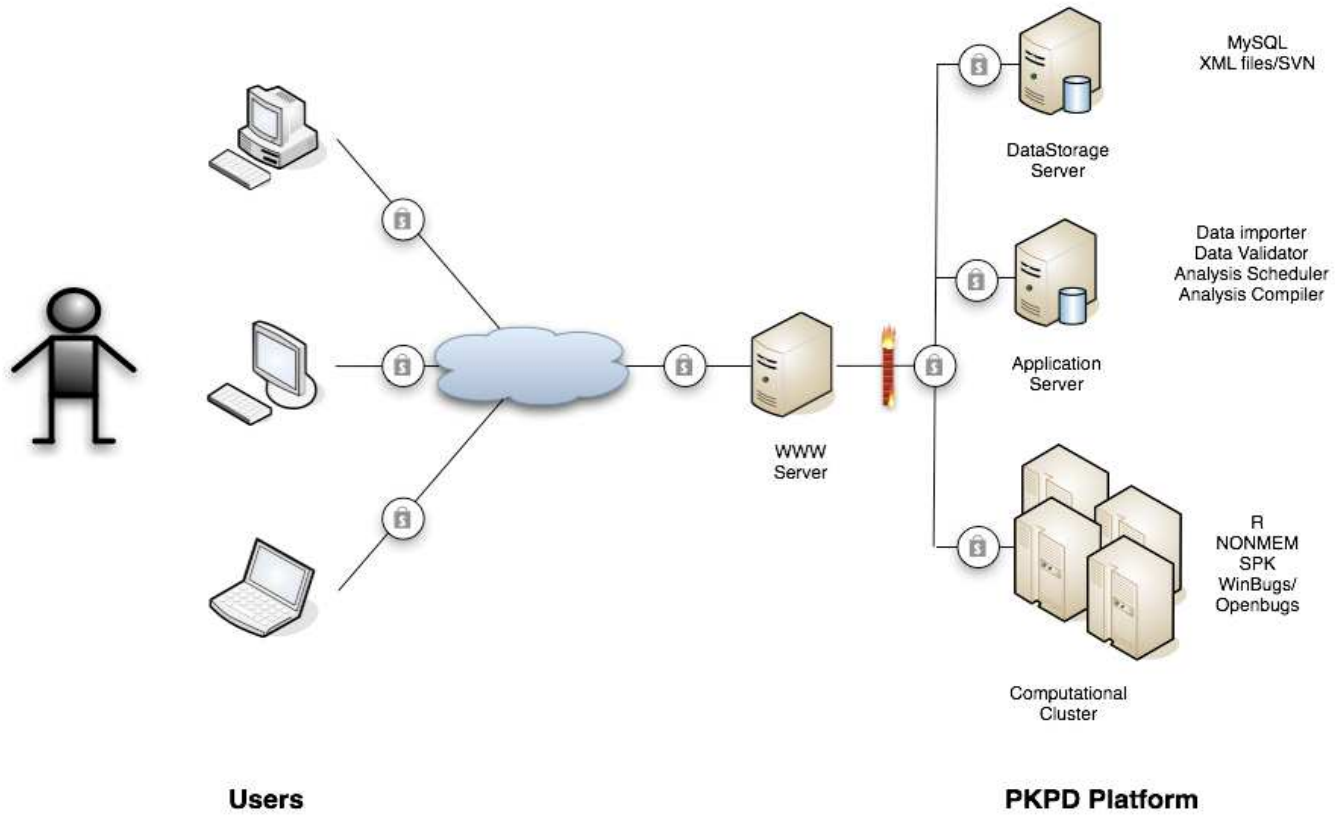
TI Pharma mechanism-based PKPD modeling platform the operation

- Development of mechanism-based PK-PD models on basis of existing data
- Strict data access restrictions
- Centralized computing network facility for data management and analysis
- Model library interface for users

TI Pharma mechanism-based PK-PD modeling platform the information flow



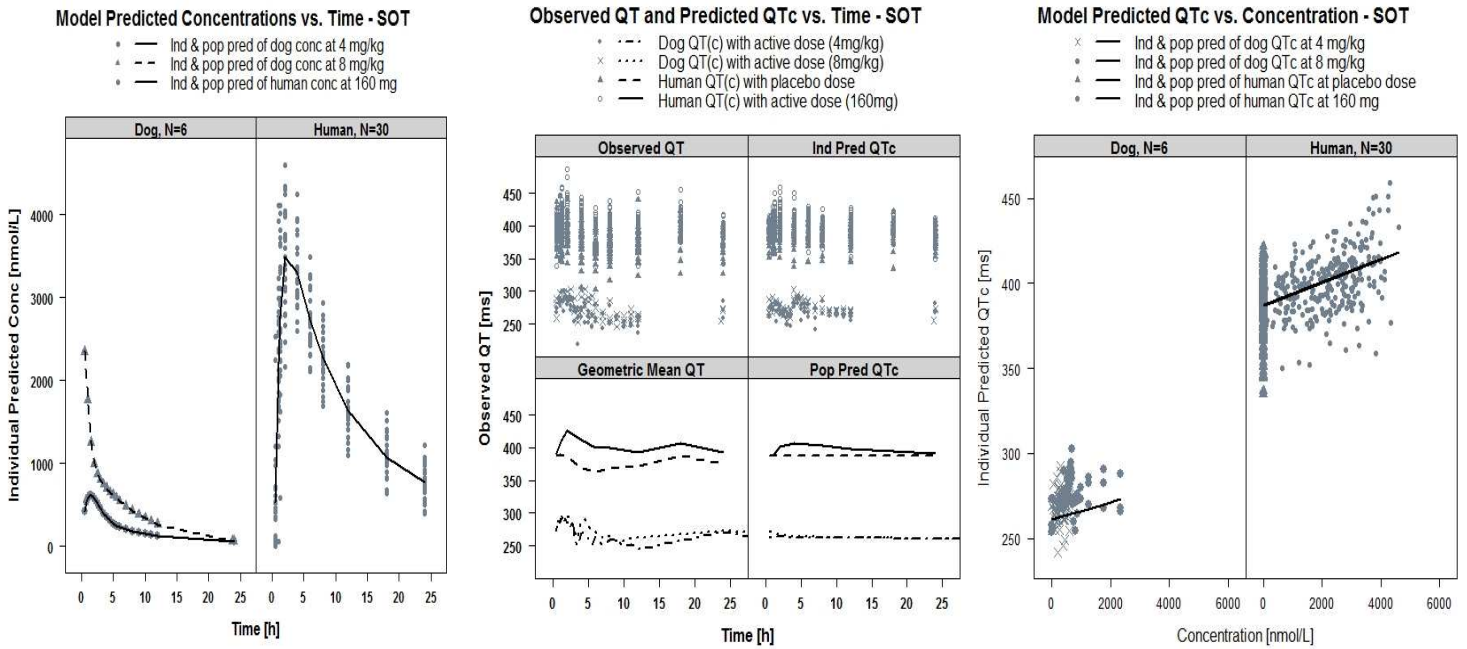
TI Pharma mechanism-based PK-PD modeling platform the database system



Prediction of pharmacology in man
cardiovascular safety

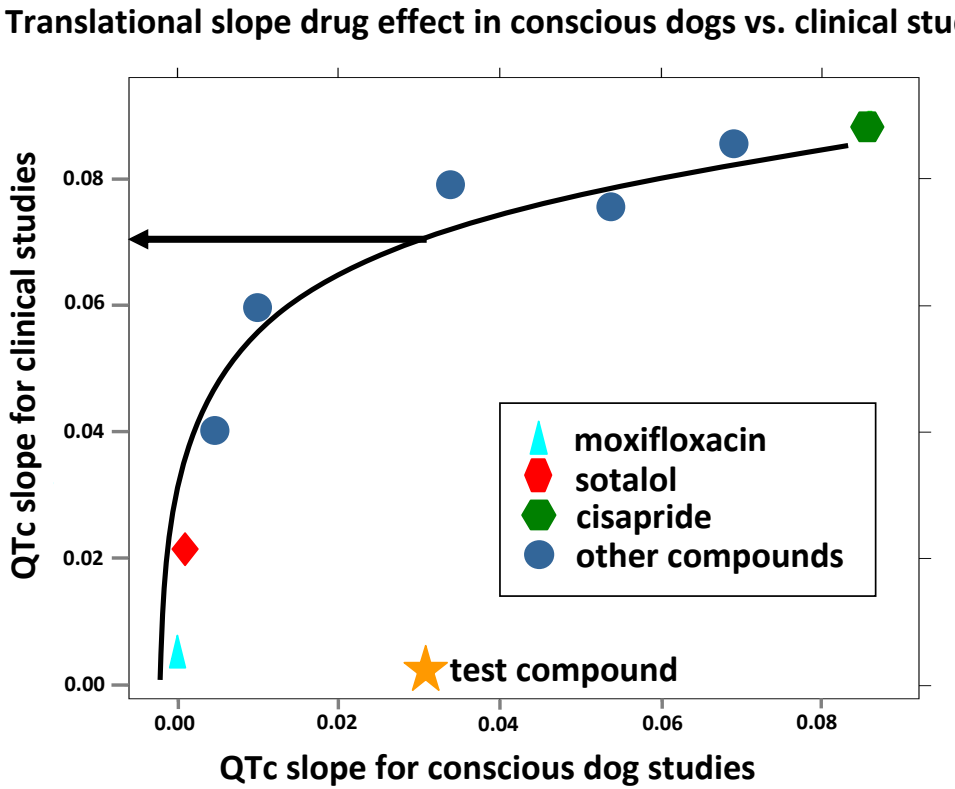
Drug		N	Dose	Variables used for modelling & simulation and sampling scheme
Moxifloxacin		4	3, 10, 30 mg/kg	Clock time, RR, QT over 24 h plasma PK from literature
		137	400mg	Clock time, RR, QT, plasma PK over 24 h
Sotalol		4	4, 8 mg/kg	Clock time, RR, QT over 48h, plasma PK literature
		30	160 mg	Clock time, RR, QT, plasma PK over 24 h
Cisapride		4	0.6, 2, 6 mg/kg	Clock time, RR, QT, plasma PK over 24 h, plasma PK from literature
		24	10, 20, 40, 80 mg	Clock time, RR, QT, plasma PK over 24 h
NCE		4	1.5 µg	Clock time, RR, QT, plasma PK over 24 h,
		24	1.5 µg	Clock time, RR, QT, plasma PK over 24 h

Animal to human extrapolation of in vivo concentration-effect relations



$$QTc = QT_0 \times RR^{\alpha} \cdot (1 + A \cdot \cos(2\pi/24 \cdot (clocktime - \varphi)) + slope \cdot C)$$

Indentifying the animal to human translation function for QTc interval prolongation



Prediction of cardiovascular risk in real life situations not in trial simulation

QTc = baseline + drug effect + co-morbidities + co-medications + ε

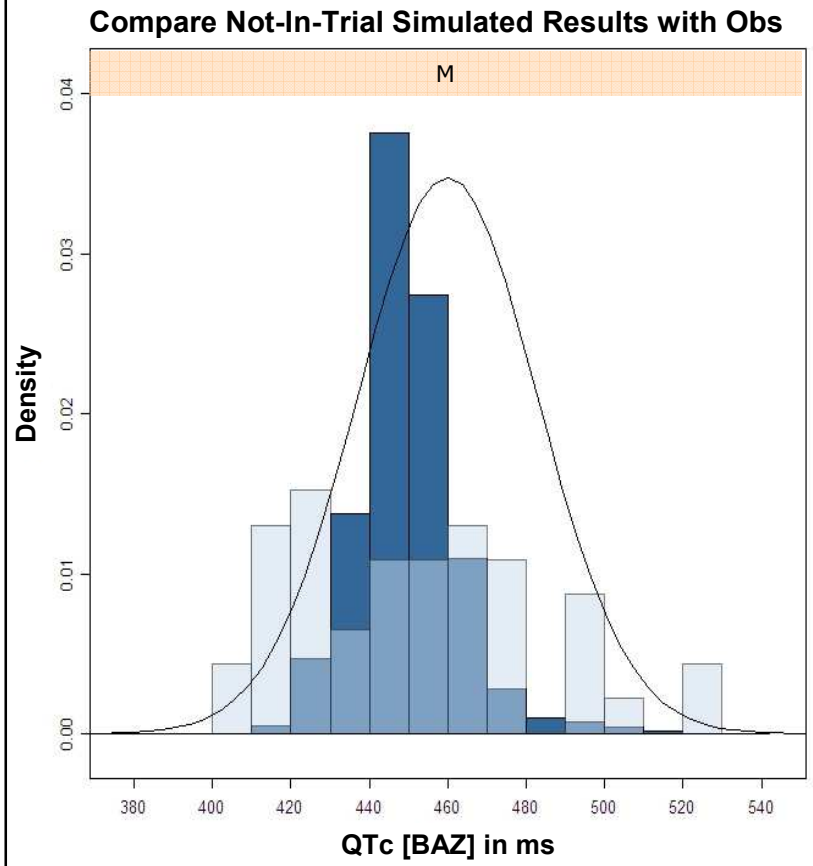
"Rotterdam study"

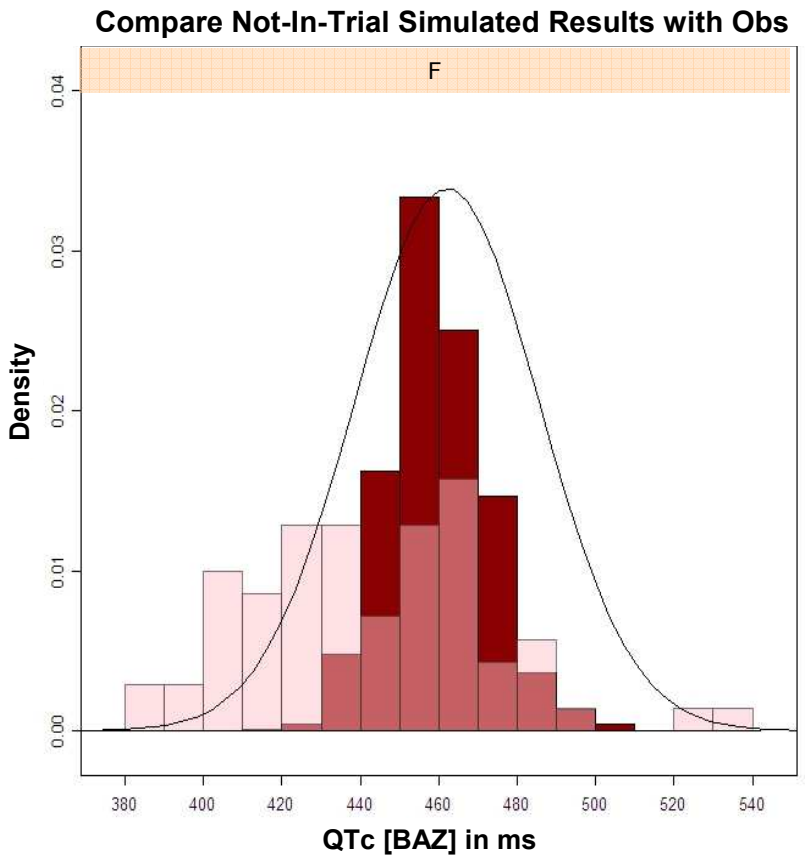
- Baseline = sex; linear increase with age
- Co-morbidities = heart failure, MI, diabetes
- Co-medication = anti-arrhythmics
- Between subject variability

Drug effect

$$QT_c = QT_0 \times RR^{\alpha} \cdot (1 + A \cdot \cos(2\pi/24 \cdot (\text{clocktime} - \varphi)) + \text{slope} \cdot C)$$

Prediction of cardiovascular risk in real life situations not in trial simulation



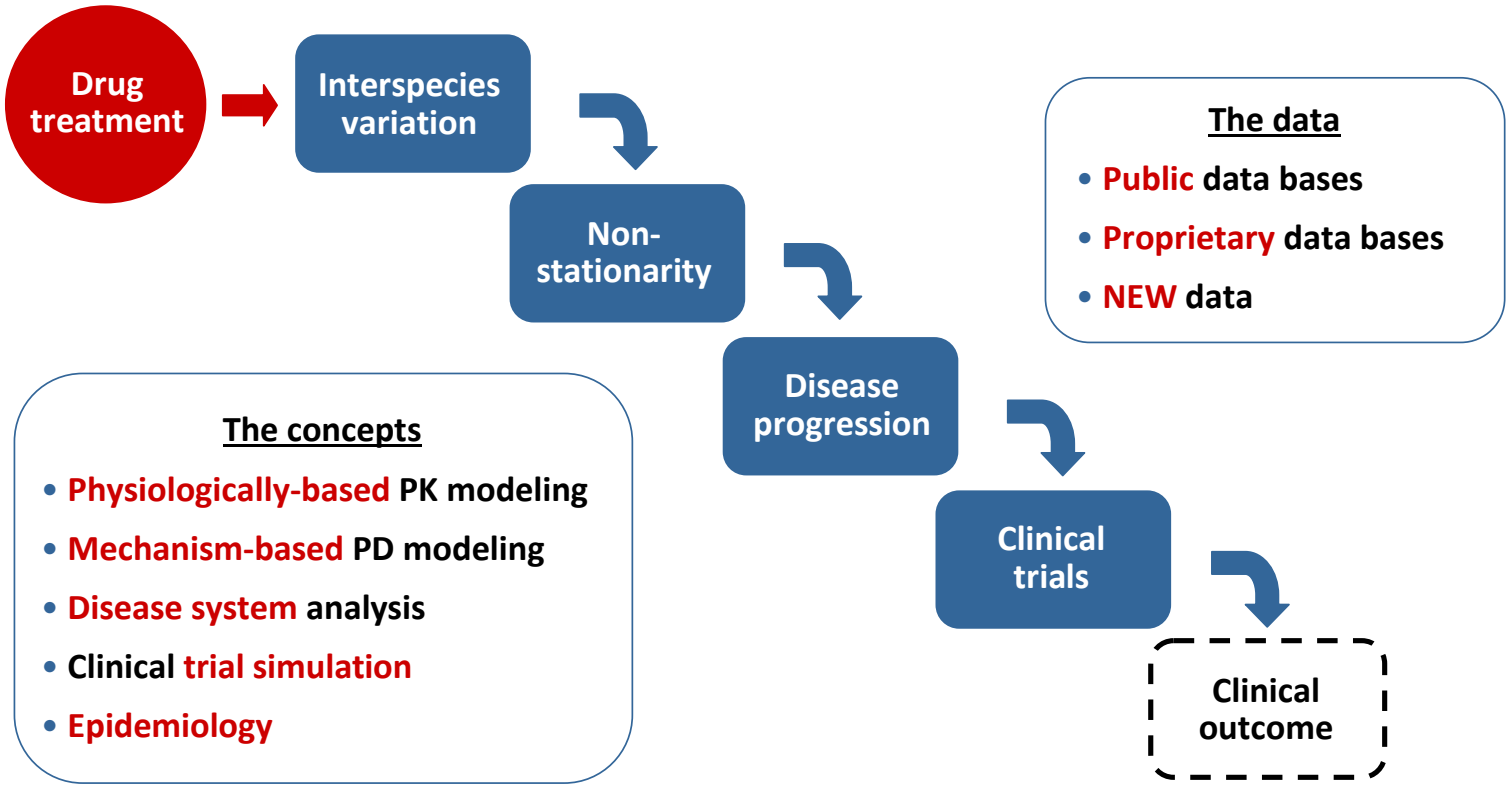


Prediction of cardiovascular risk
from ECG findings to sudden cardiac death

- Not in trial simulation to predict natural variation in QTc in the target population
- Analyze relationship between variation in QTc and cardiovascular risk in the target population
  - Delta analysis
  - Threshold analysis
- Develop and incorporate cardiovascular risk prediction model

Prediction of cardiovascular risk

Quantitative Systems Pharmacology
utility of collaborative data resources



Drug & Disease Model Resource (DDMoRe)
vision and deliverables