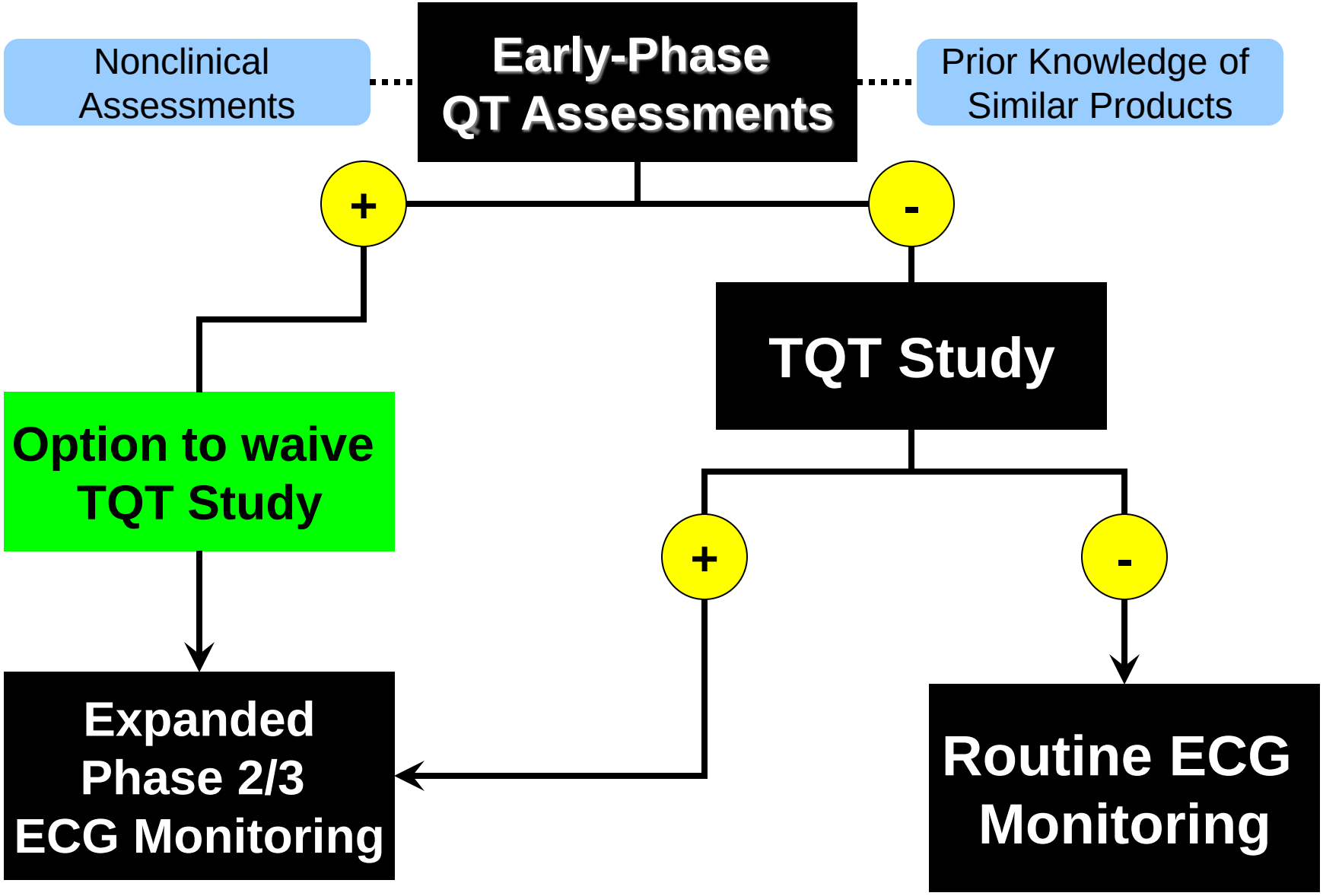
Session I: Role of Concentration Effect Modeling in Assessing a Drug's Effect on the QTc Interval

Applications of C-QT Modeling

- Predict the QTc effects of lower doses, dosing regimens, routes of administration, or formulations not evaluated in TQT study
- Predict the QTc effects of intrinsic and extrinsic factors that affect PK to support dose adjustments
- Clarify ambiguous results in TQT study
- Obviate the TQT study for drugs with QT prolongation or shortening in phase 1 studies

TQT Study Decision Tree



Challenges with Early Phase 1 QT Assessment

- Lack of assay sensitivity
- Lack of standardized ECG collection
- Limited clinical pharmacology profile
- Small trials
  - Reduced power to exclude small increases in QTc using E14 statistical method

Challenges Using C-QT Analysis to Exclude Small QTc Effects

- Evidence to support the lack of C-QT relationship
- Lack of pre-specification of model structure and modeling methods
- Impact of model misspecification

Session 1 Agenda

- FDA statistical perspective
  - Joanne Zhang, Ph.D.
- Statistical framework of C-QT model
  - Günter Heimann, Ph.D.
- Power of detecting moxifloxacin response in small clinical trials using C-QT model
  - Georg Ferber, Ph.D.
- Industry experience of applying C-QT analysis in phase 1 studies
  - Pfizer Experience, Steve Riley, Pharm.D., Ph.D.
  - AstraZeneca Experience, Corina Dota, M.D.
- Round table discussion

Breakout Session 1

- Moderators: Christine Garnett, Steve Riley
- Key Question:
  - What work remains to be done to convincingly demonstrate that C-QT modeling applied to early clinical data can exclude mild QTc prolongation with the same level of confidence as the E14 ‘time-matched QTc analysis’?