Evaluation of assumptions underpinning pharmacometric models

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Models and assumptions

- All models are underpinned by assumptions
- The validity of model inference depends on:
  - Appropriateness
  - Likely impact of the underlying assumptions

Importance of assumption evaluation

Guidance for Industry Population Pharmacokinetics

FDA. 1999; https://www.fda.gov/downloads/drugs/guidances/UCM072137.pdf

Guideline on Reporting the Results of Population Pharmacokinetic Analyses

EMEA. 2007; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003067.pdf

Good Practices in Model-Informed Drug Discovery and Development: Practice, Application, and Documentation

EFPIA MID3 Workgroup et al., CPT Pharmacometrics Syst Pharmacol. 2016;5(3):93-122

Other published guidelines

Inadequate documentation and evaluation of assumptions

- Assumptions are not routinely addressed in published literature
- Regulatory perspective (EMA/EFPIA M&S workshop in 2011):
  - Limitation of analysis submitted for regulatory review
  - A lack of transparent description of influential assumptions
- Barrier for effective model use and regulatory review

EFPIA MID3 Workgroup et al., CPT Pharmacometrics Syst Pharmacol. 2016;5(3):93-122

Existing framework

1

WHITE PAPER

Good Practices in Model-Informed Drug Discovery and Development: Practice, Application, and Documentation

EFPIA MID3 Workgroup: SF Marshall[1]*, R Burghaus[2], V Cosson[3], SYA Cheung[4], M Chenel[5], O DellaPasqua[6], N Frey[3], B Hamrén[7], L Harnisch[1], F Ivanow[8], T Kerbusch[9], J Lippert[2], PA Milligan[1], S Rohou[10], A Staab[11], JL Steimer[12], C Tornøe[13] and SAG Visser[14]

EFPIA MID3 Workgroup et al., CPT Pharmacometrics Syst Pharmacol. 2016;5(3):93-122

2

Assumption Testing in Population Pharmacokinetic Models: Illustrated with an Analysis of Moxonidine Data from Congestive Heart Failure Patients

Mats O. Karlsson,[1,4] E. Niclas Jonsson,[1] Curtis G. Wiltse,[2] and Janet R. Wade[3]

Karlsson et al., J Pharmacokinet Biopharm. 1998;26(2):207-46

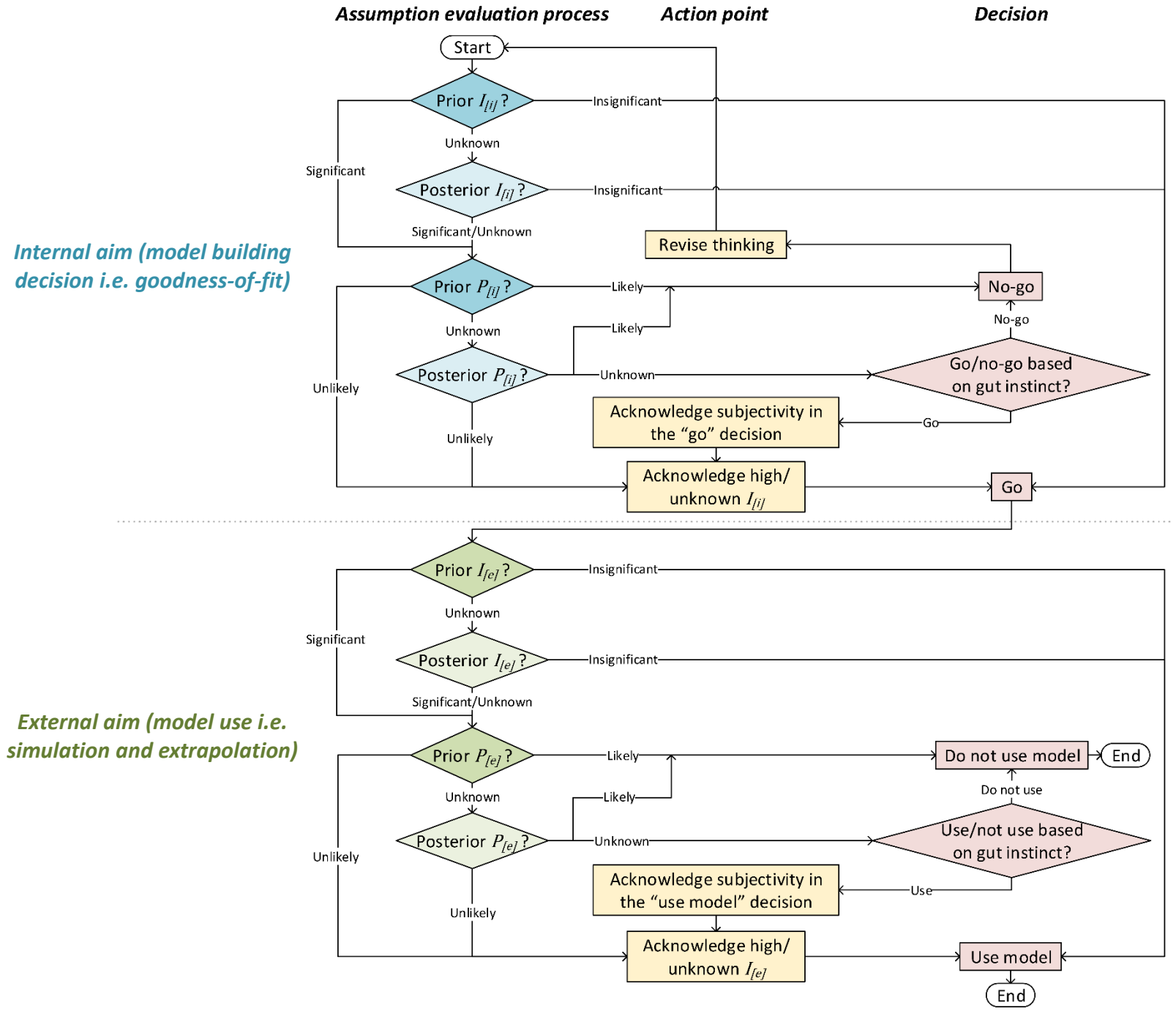
- Documentation of assumptions
- How to assess assumptions?

Aim

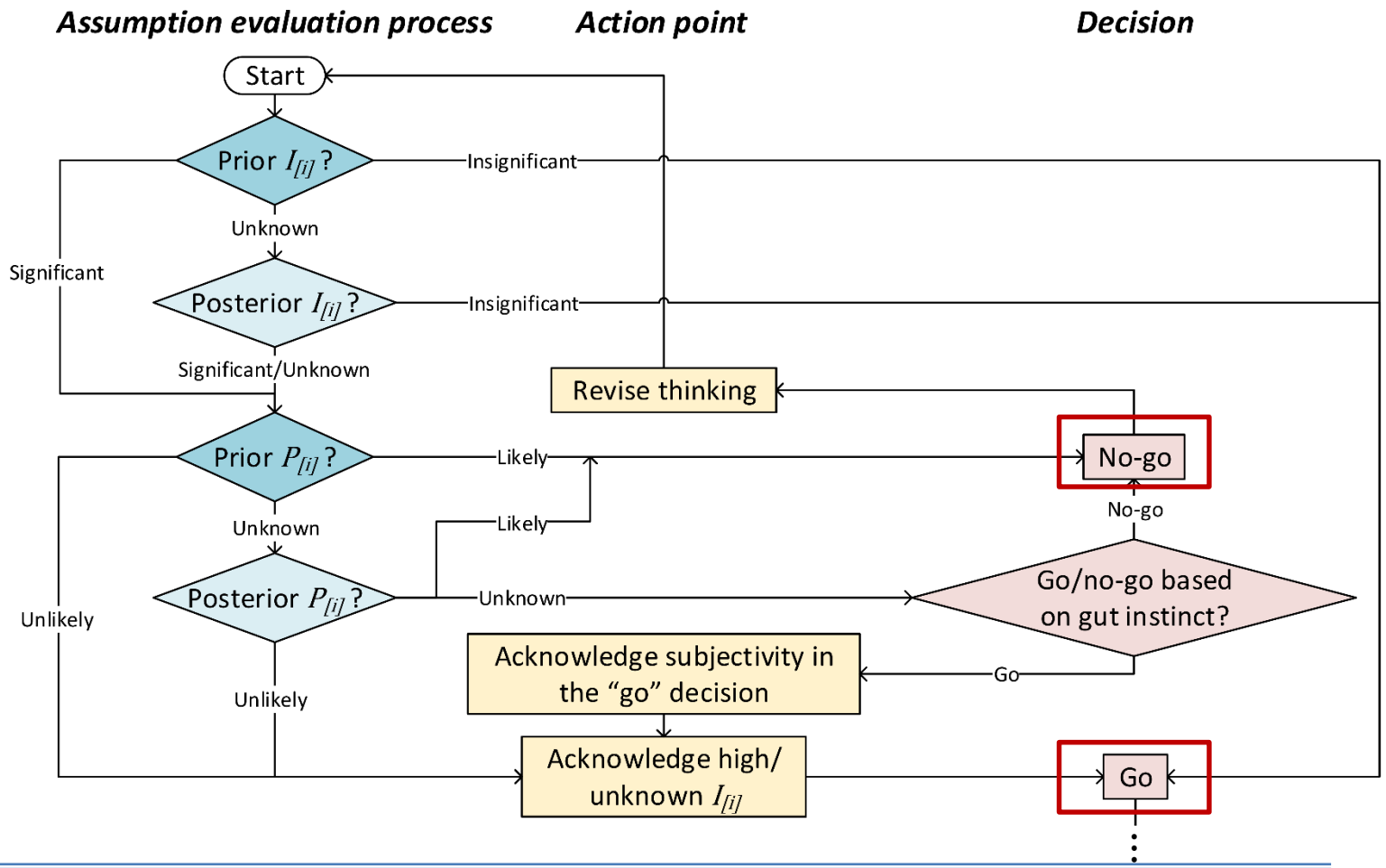
- To formalise a framework for evaluating assumptions intrinsic to a top-down or bottom-up pharmacometric model

Classification of assumptions

- According to the origin of the assumption
- Implicit:
  - Theorem-based
  - e.g. Pearson correlation → linearity
- Explicit:
  - Arises from a gap in knowledge that requires imputation
  - e.g. Heuristic solution to an unknown system → Michaelis-Menten model

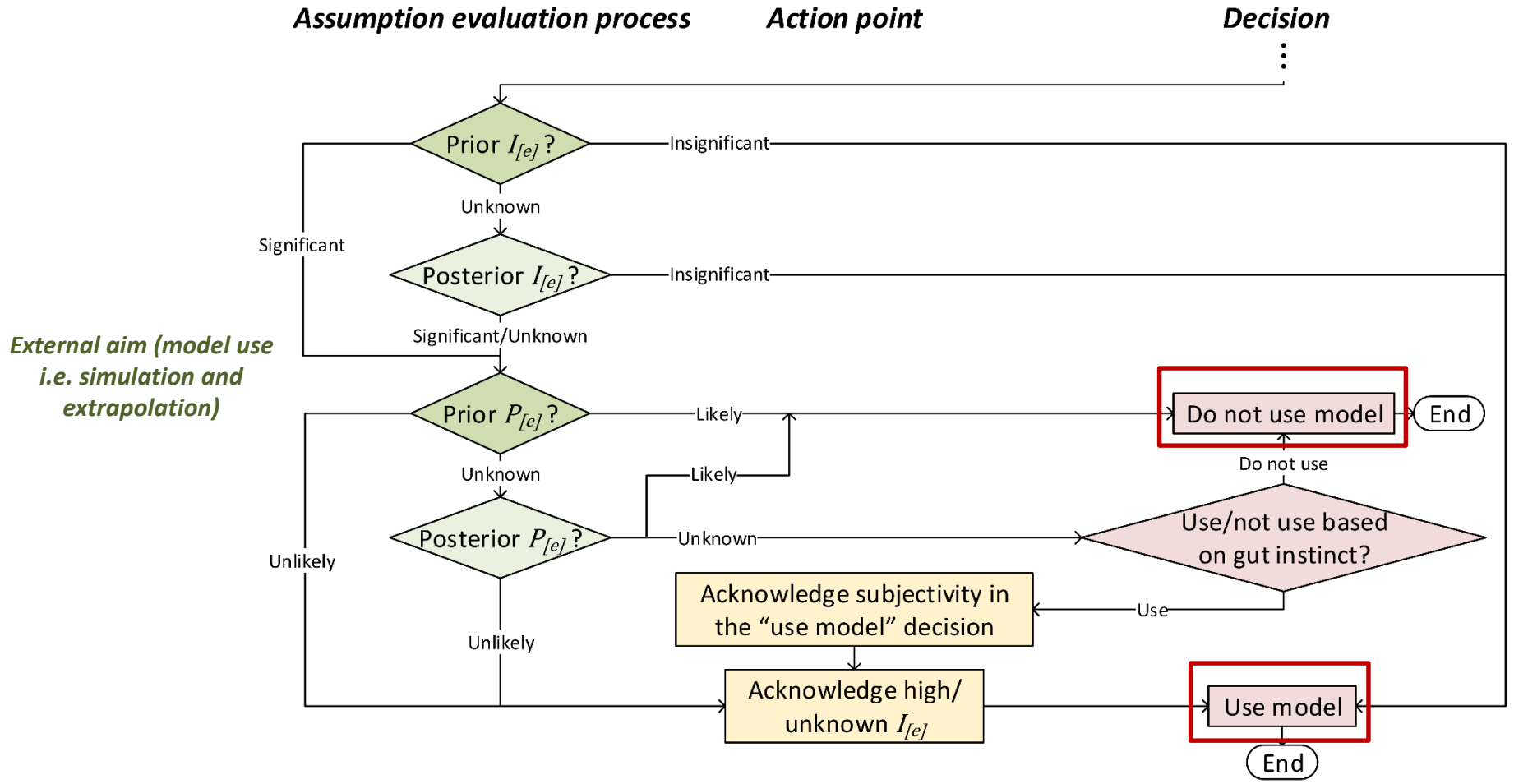

Assumption evaluation process
Action point
Decision
Internal aim (model building decision i.e. goodness-of-fit)
Start
Prior $I_{[ij]}$?
Insignificant
Unknown
Significant
Posterior $I_{[ij]}$?
Insignificant
Significant/Unknown
Revise thinking
Prior $P_{[ij]}$?
Likely
No-go
Unknown
Likely
No-go
Posterior $P_{[ij]}$?
Unknown
Go/no-go based on gut instinct?
Unlikely
Acknowledge subjectivity in the "go" decision
Go
Unlikely
Acknowledge high/ unknown $I_{[ij]}$
Go
External aim (model use i.e. simulation and extrapolation)
Prior $I_{[e]}$?
Insignificant
Unknown
Significant
Posterior $I_{[e]}$?
Insignificant
Significant/Unknown
Prior $P_{[e]}$?
Likely
Do not use model
End
Unknown
Likely
Do not use
Posterior $P_{[e]}$?
Unknown
Use/not use based on gut instinct?
Unlikely
Acknowledge subjectivity in the "use model" decision
Use
Unlikely
Acknowledge high/ unknown $I_{[e]}$
Use model
End

Evaluation against an internal aim (of model building)

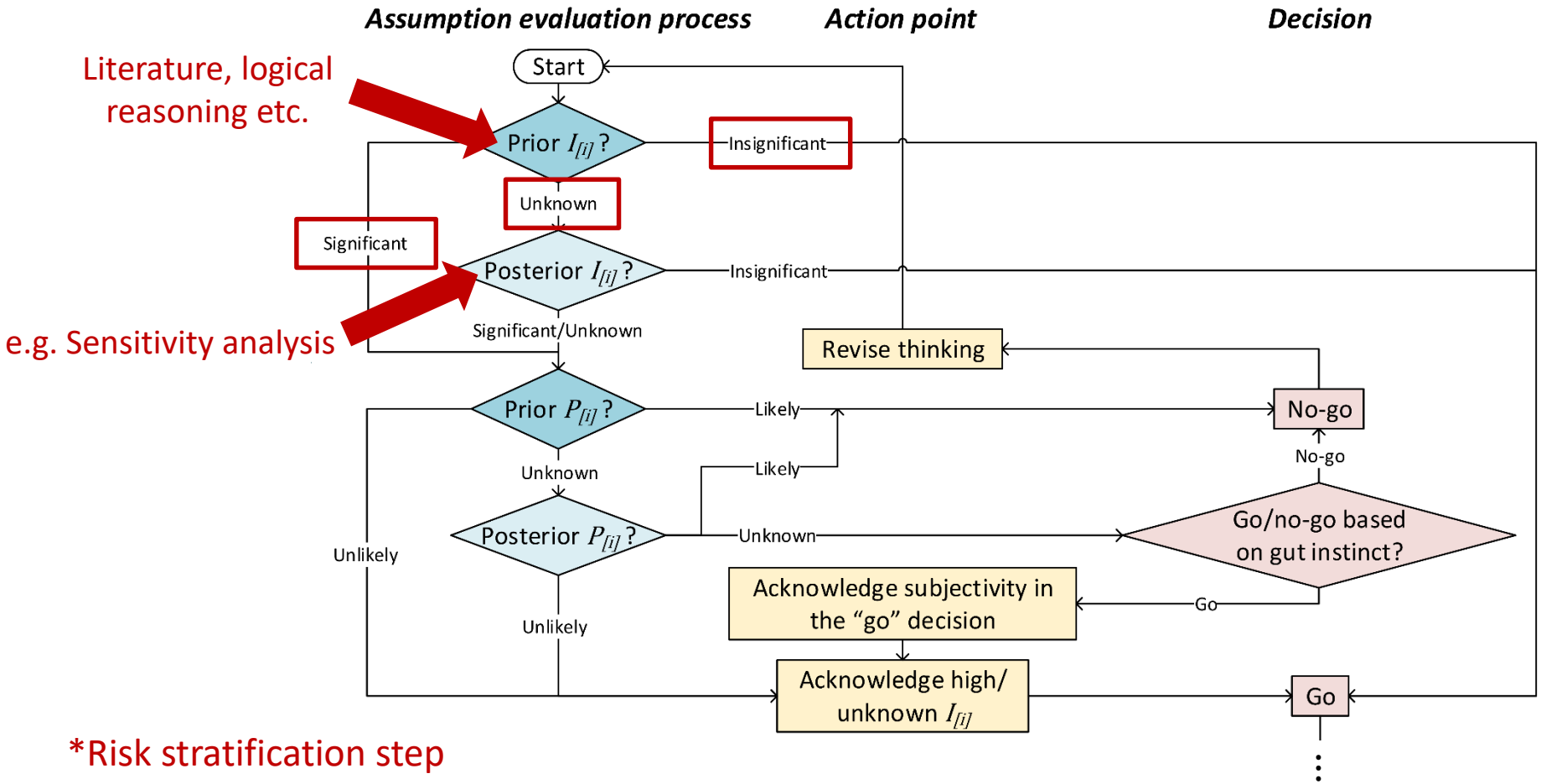


Internal aim (model building decision i.e. goodness-of-fit)

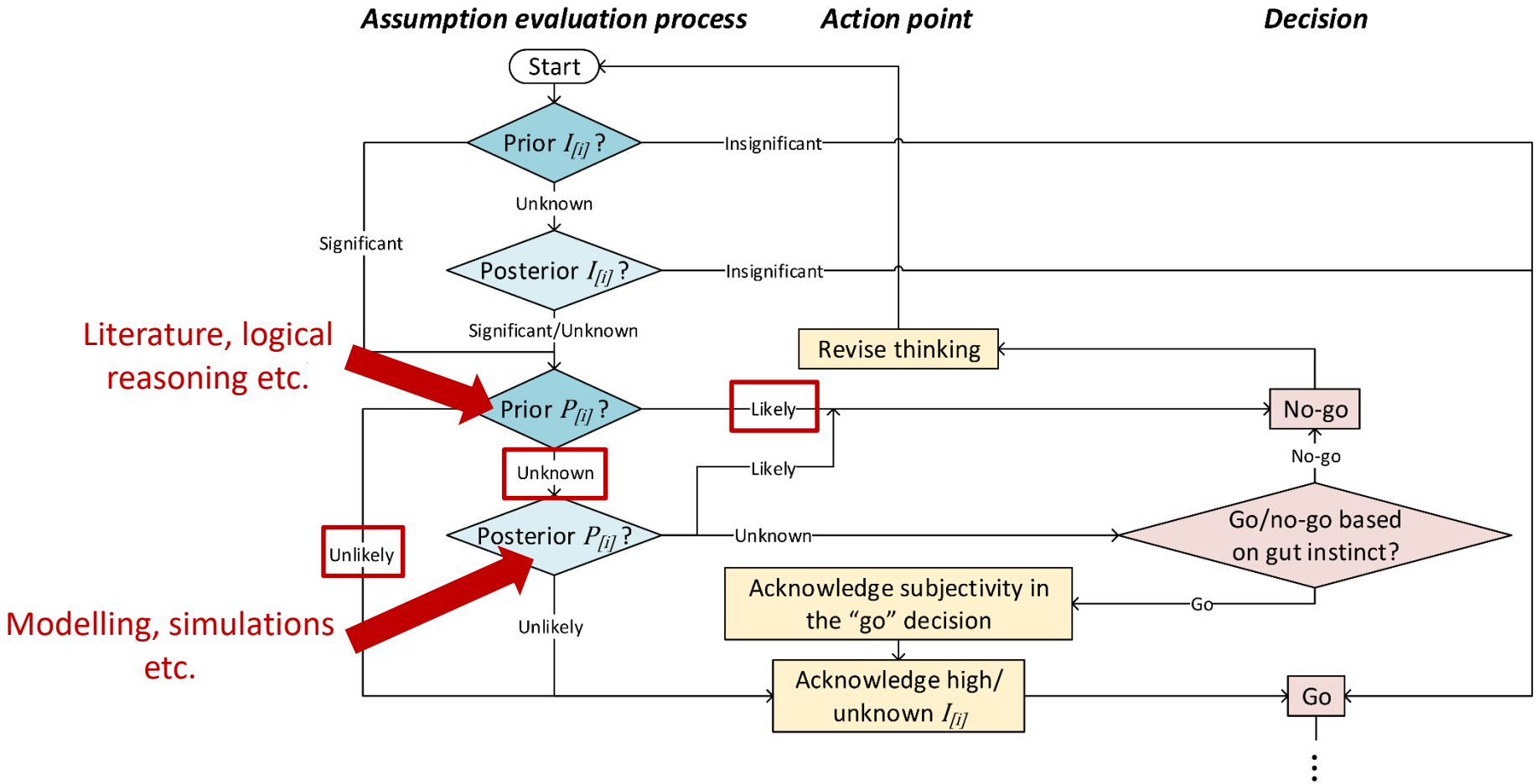
Evaluation against an external aim (i.e. model use)



Impact of assumption violation, I

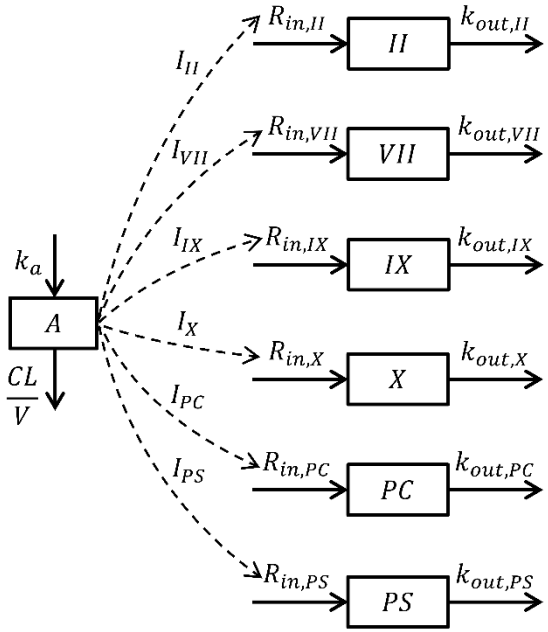


Probability of assumption violation, P



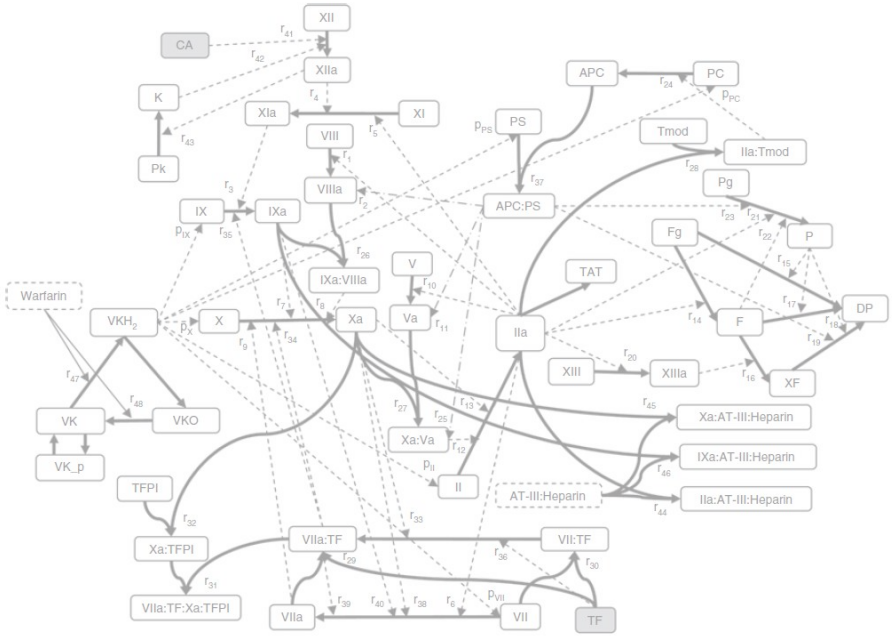
Application

- Top-down example
  - To develop a K-PD model for warfarin and vitamin K-dependent coagulation proteins



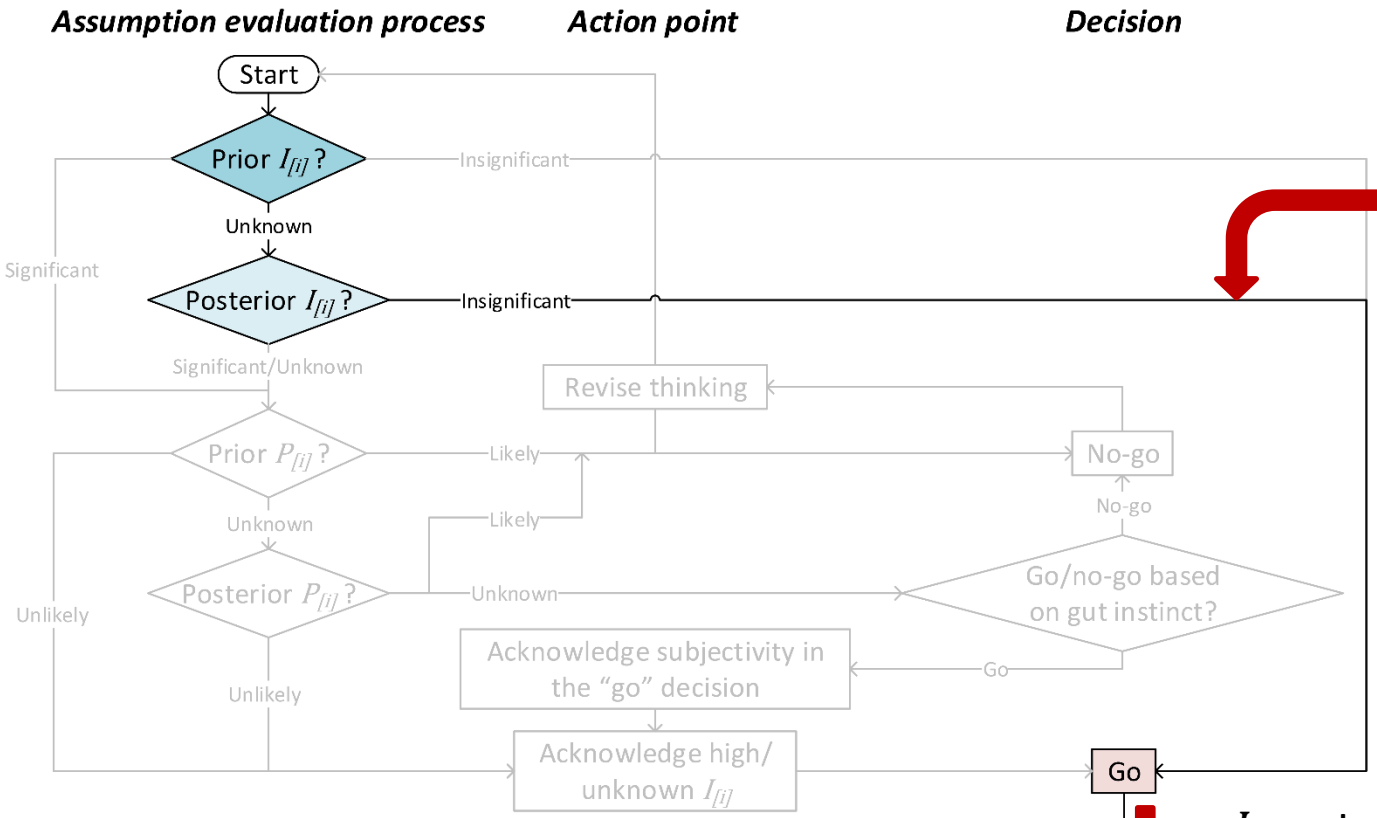
Ooi et al., Clin Pharmacokinet. 2017; 56(12):1555-66

- Bottom-up example
  - Factor VII-based method for INR prediction based on a QSP coagulation network model



Wajima et al., Clin Pharmacol Ther. 2009;86(3):290-8

Explicit assumption: Daily dose time of 6pm



Sensitivity analysis	
Imputed daily dose time	**OFV**
8 a.m.	5298
12 p.m.	5298
4 p.m.	5298
6 p.m.	5298
8 p.m.	5298

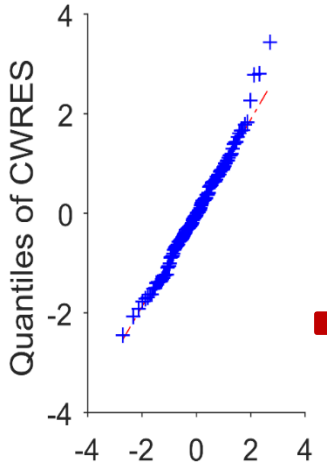
$I_{[i]}$ = Insignificant

Decision (model building) = **Go**

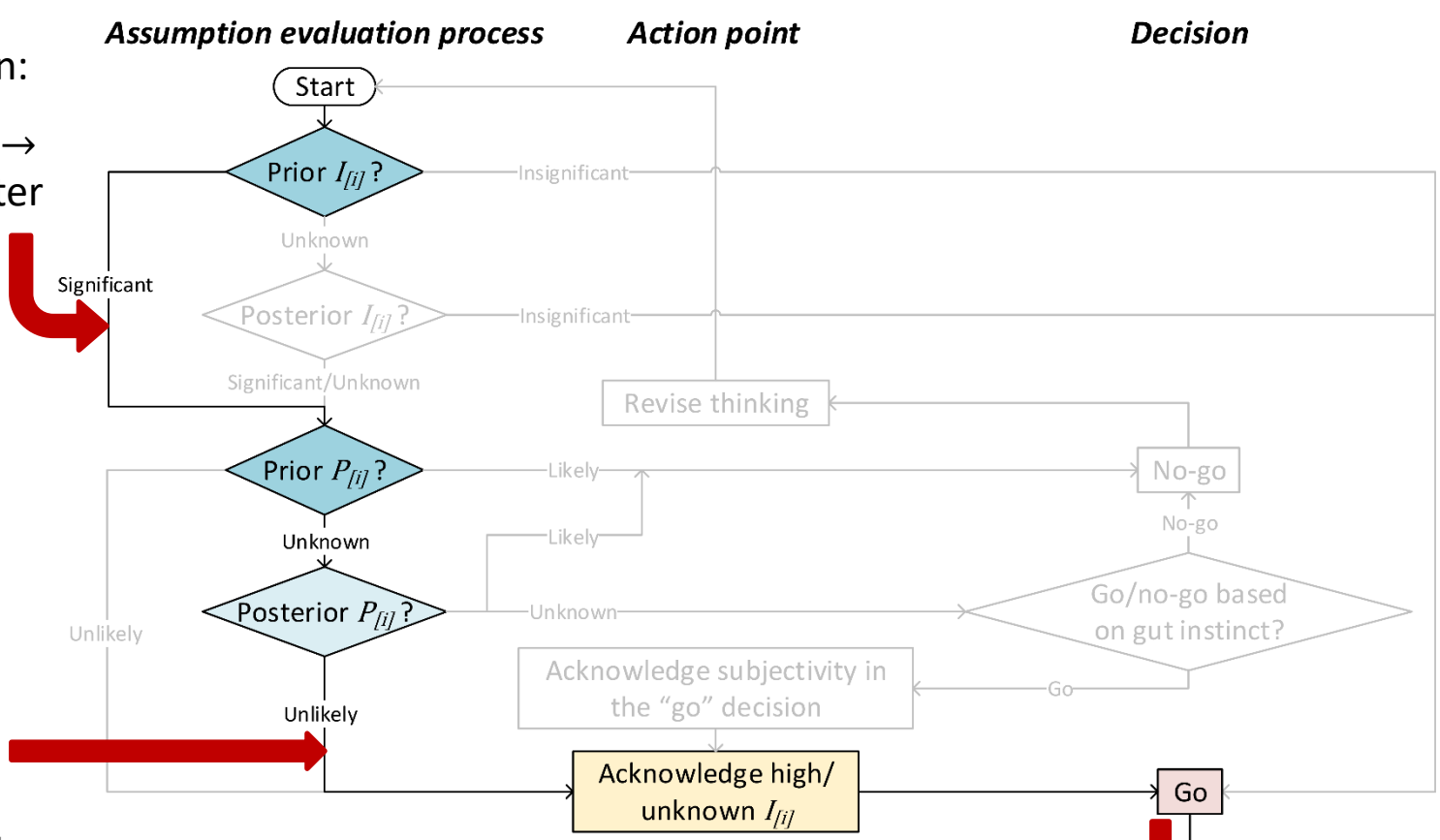
Implicit assumption: $\varepsilon \sim N(0, \sigma^2)$

Model misspecification:

Non-normality → biased parameter estimates



KS test: $p = 0.998$



$I_{[i]}$ =Significant, $P_{[i]}$ = Unlikely

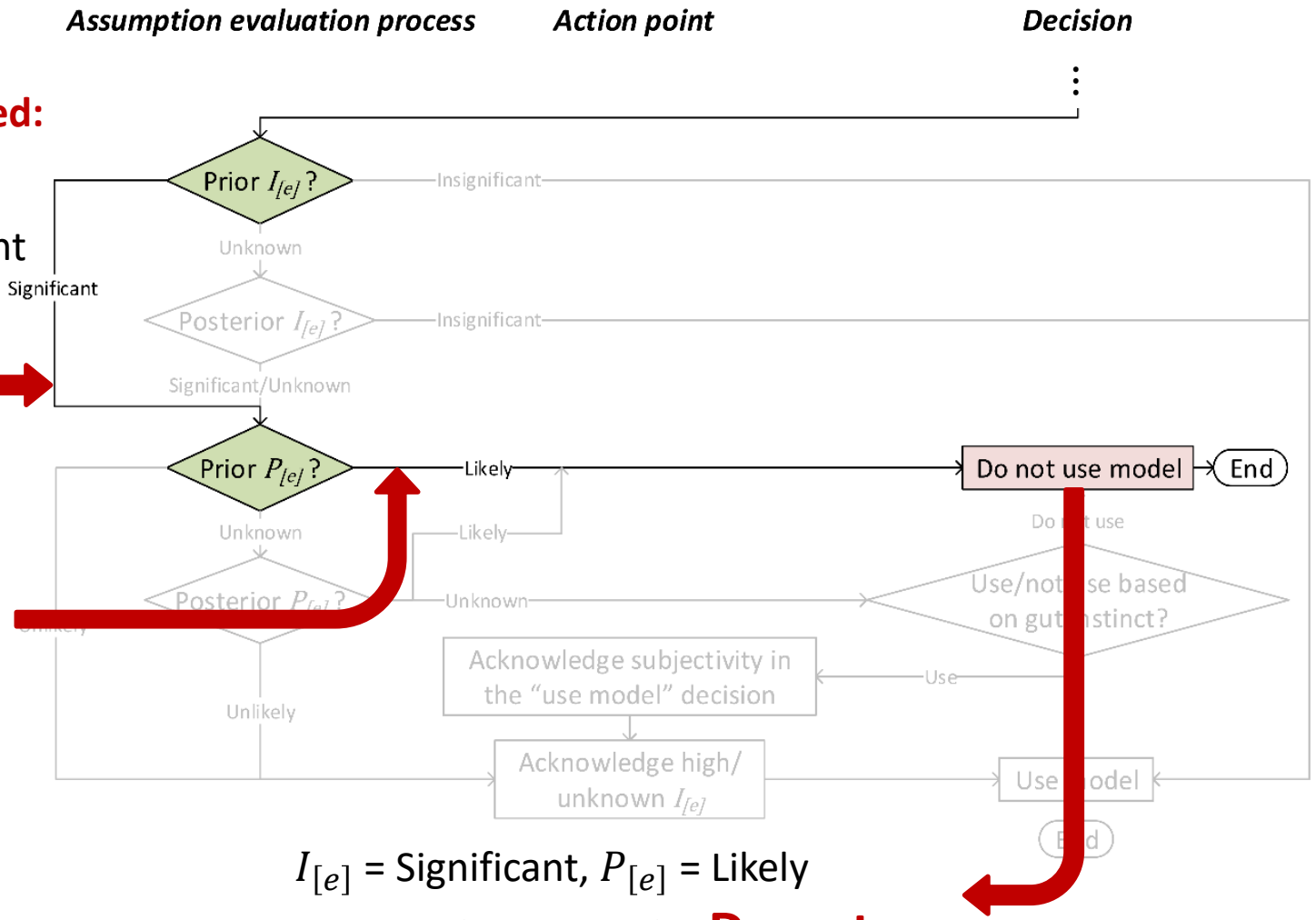
Decision (model building) = **Go**

Assumption: Linear PD model (External aim)

Predicting factor levels beyond the dose range modelled:

ER relationship is nonlinear → different predictions

Empirical nature of the linear model → extrapolation: predictions likely biased



$I_{[e]}$ = Significant, $P_{[e]}$ = Likely

Decision (model use) = **Do not use**

Discussion

- A flowchart for systematic evaluation of assumptions is proposed
- Application to top-down (and bottom-up) models
- The next step:
  - Apply the flowchart to other settings
  - To fully assess its applicability and practicality in assumption evaluation

Acknowledgements

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