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:
  - Probability
  - Impact of assumption violation
- The boundary beyond which the use of an assumption is invalid → limitation

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 reporting of assumptions

- Assumptions are not addressed routinely 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 **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

Recommendations:

- Documentation of assumptions
- How to assess assumptions?

2 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

Aim

- To propose a framework for evaluating assumptions inherent to a top-down or bottom-up pharmacometric model

Classification of assumptions

- Identification of assumptions → according to the **origin** of the assumption
- Implicit:
  - Arise from an **inherent component** of a method or model

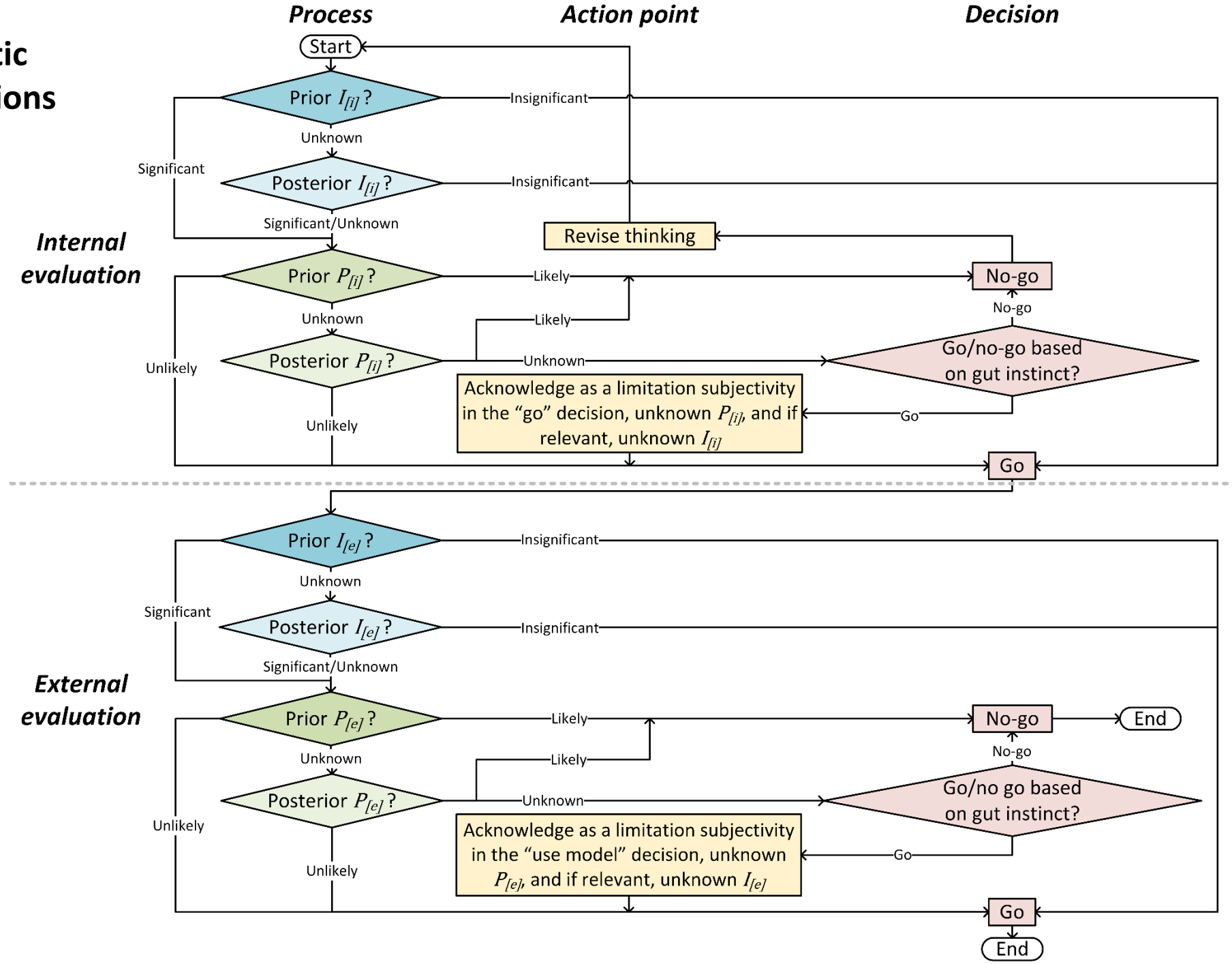
    e.g. Cockcroft-Gault equation implicitly assumes serum creatinine is at steady-state

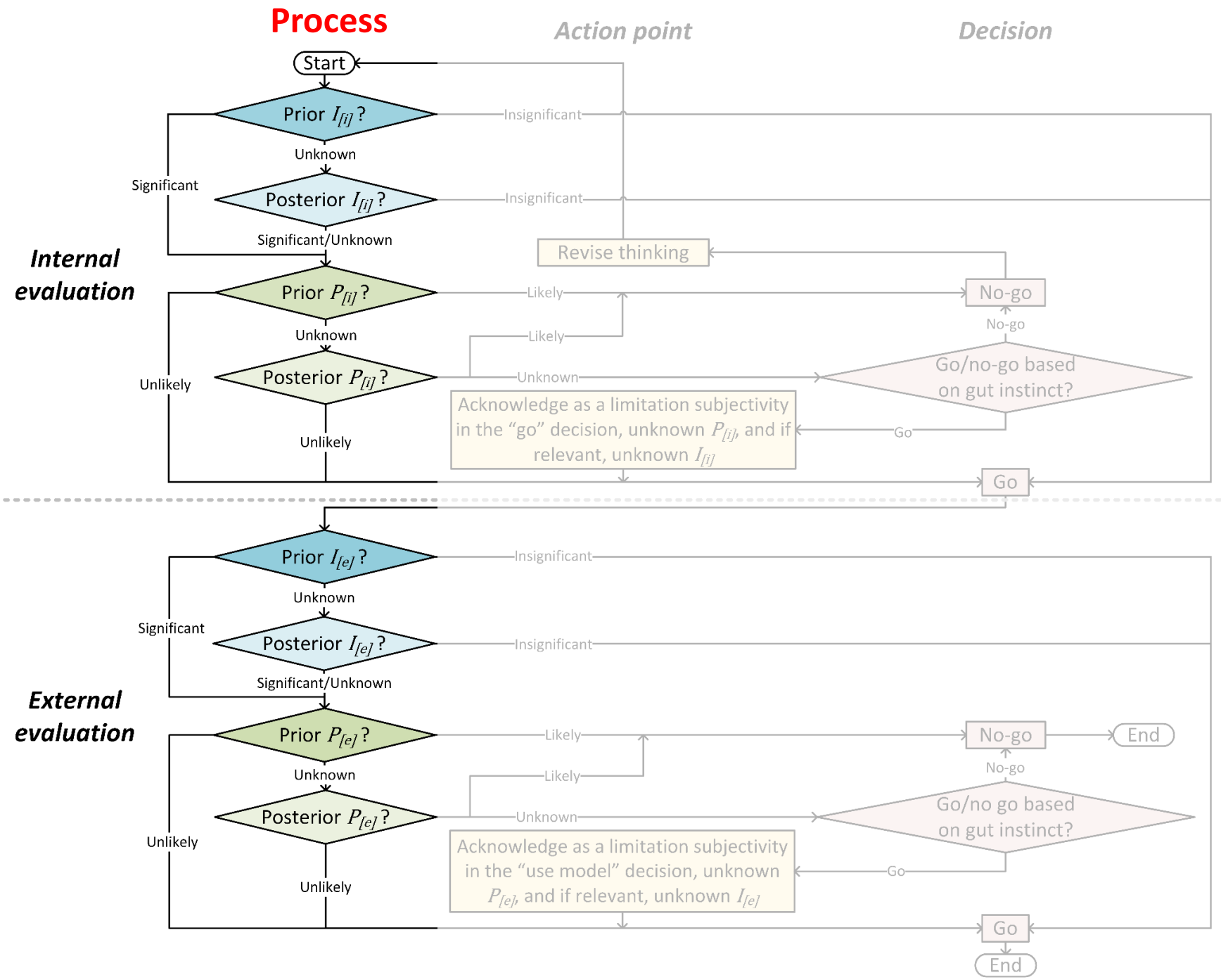
    e.g. Maximum likelihood method typically requires the observations to be iid
- Explicit:
  - Arise from the **application** of a method or model

    e.g. Cockcroft-Gault equation provides an unbiased estimate of mGFR

    e.g. The recorded blood sampling times are accurate

Flowchart for systematic evaluation of assumptions




Process
Action point
Decision
Internal evaluation
Start
Prior $I_{[i]}$?
Insignificant
Unknown
Significant
Posterior $I_{[i]}$?
Insignificant
Significant/Unknown
Revise thinking
Prior $P_{[i]}$?
Likely
No-go
Unknown
Likely
No-go
Unlikely
Posterior $P_{[i]}$?
Unknown
Go/no-go based on gut instinct?
Acknowledge as a limitation subjectivity in the "go" decision, unknown $P_{[i]}$, and if relevant, unknown $I_{[i]}$
Go
Unlikely
Go
External evaluation
Prior $I_{[e]}$?
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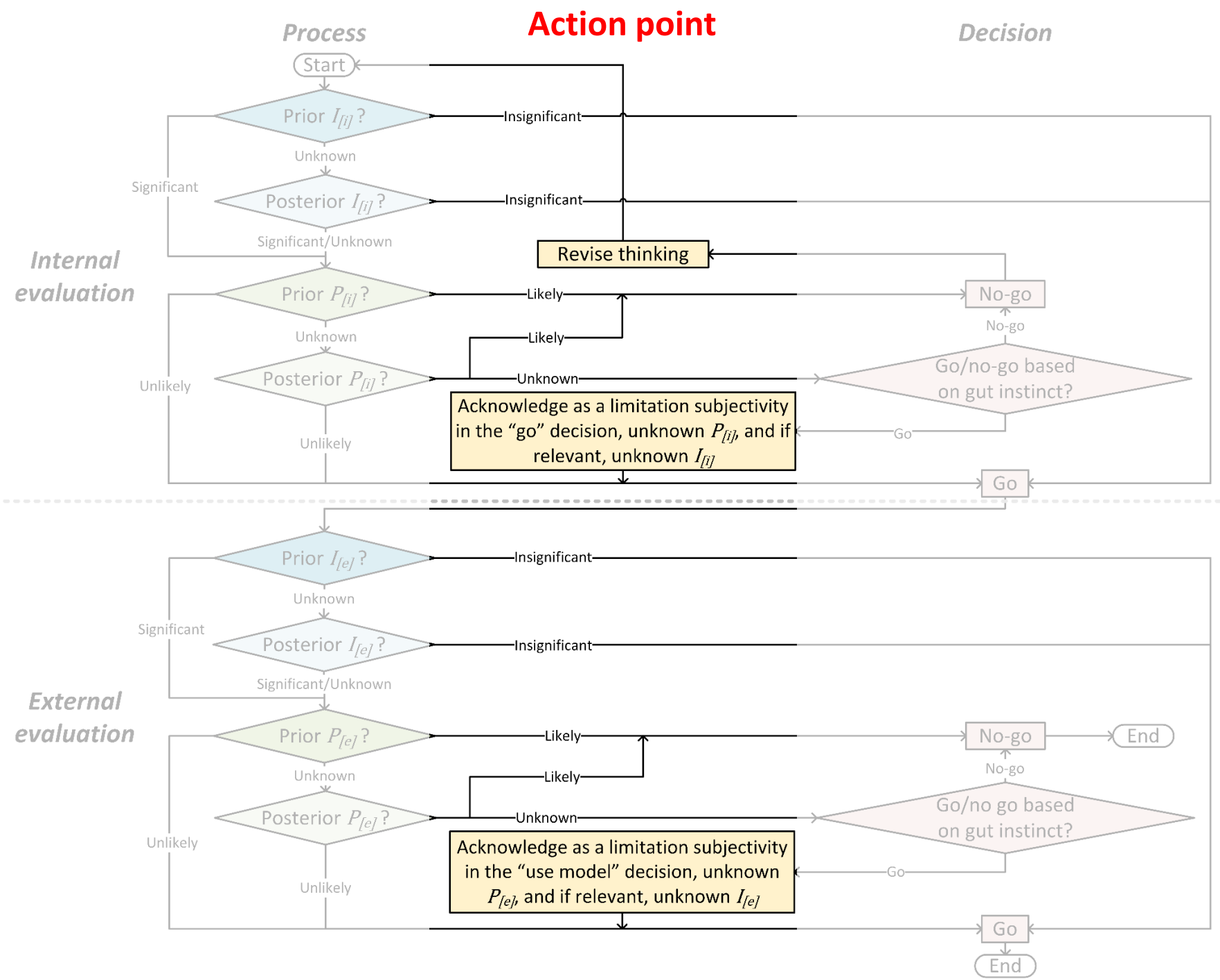
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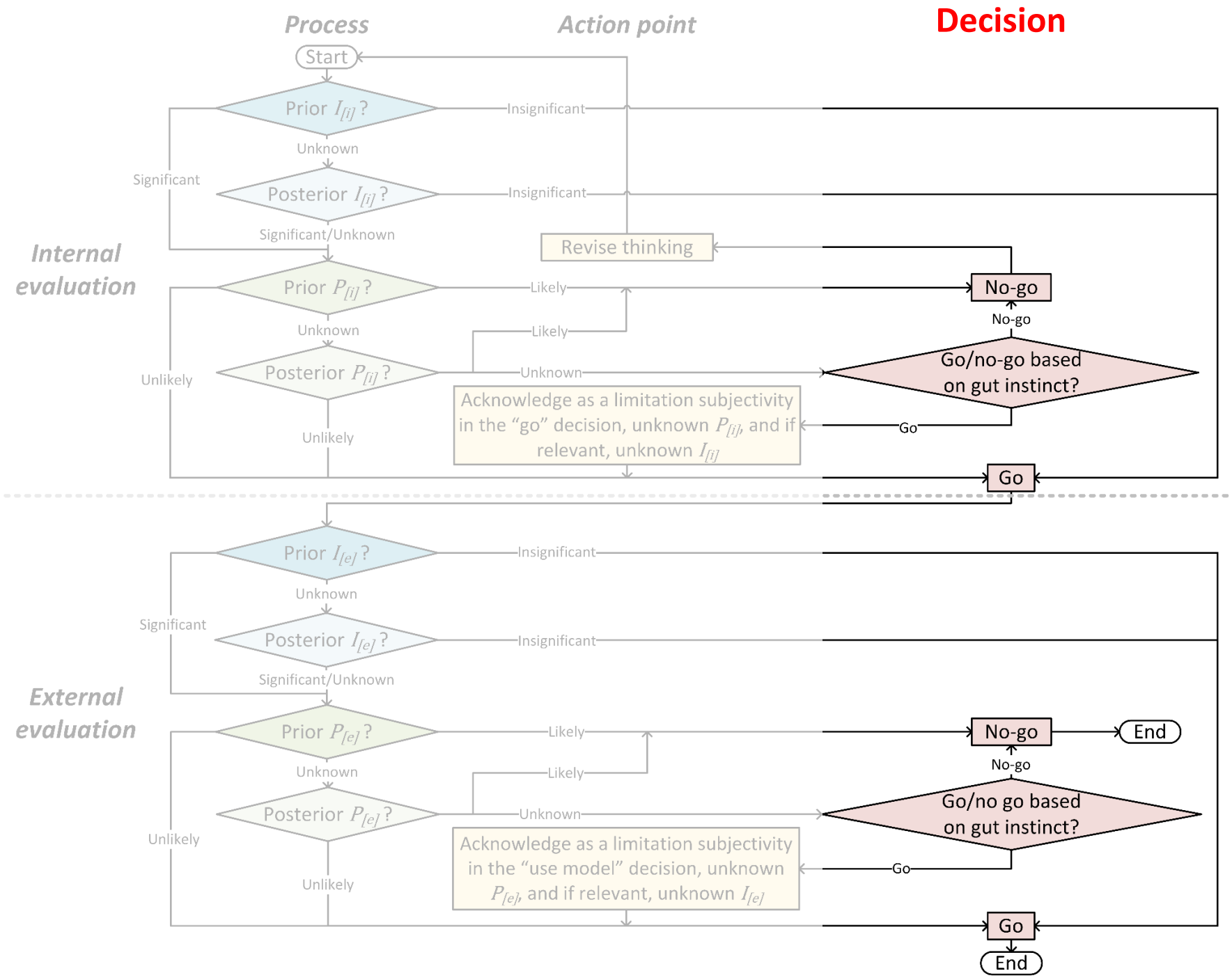
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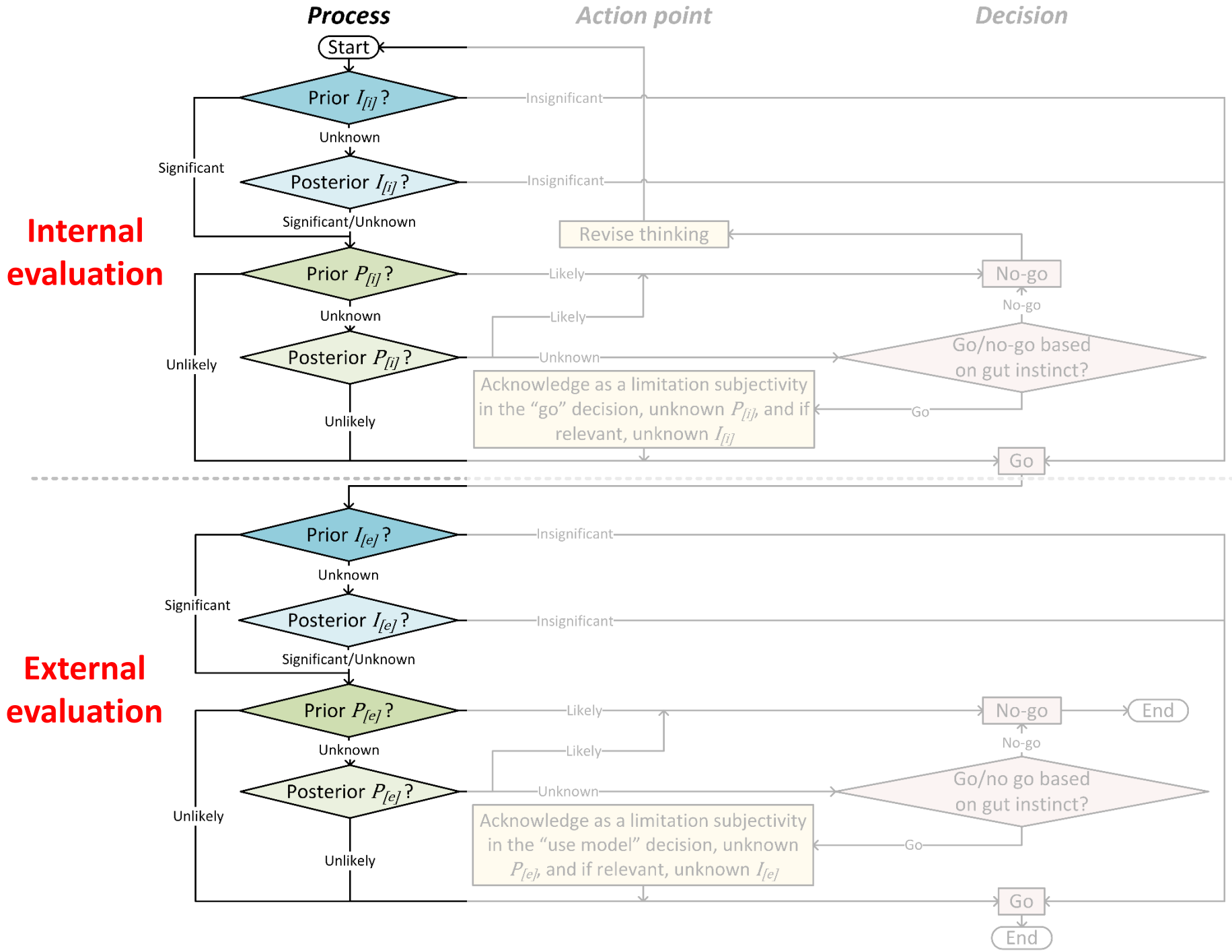
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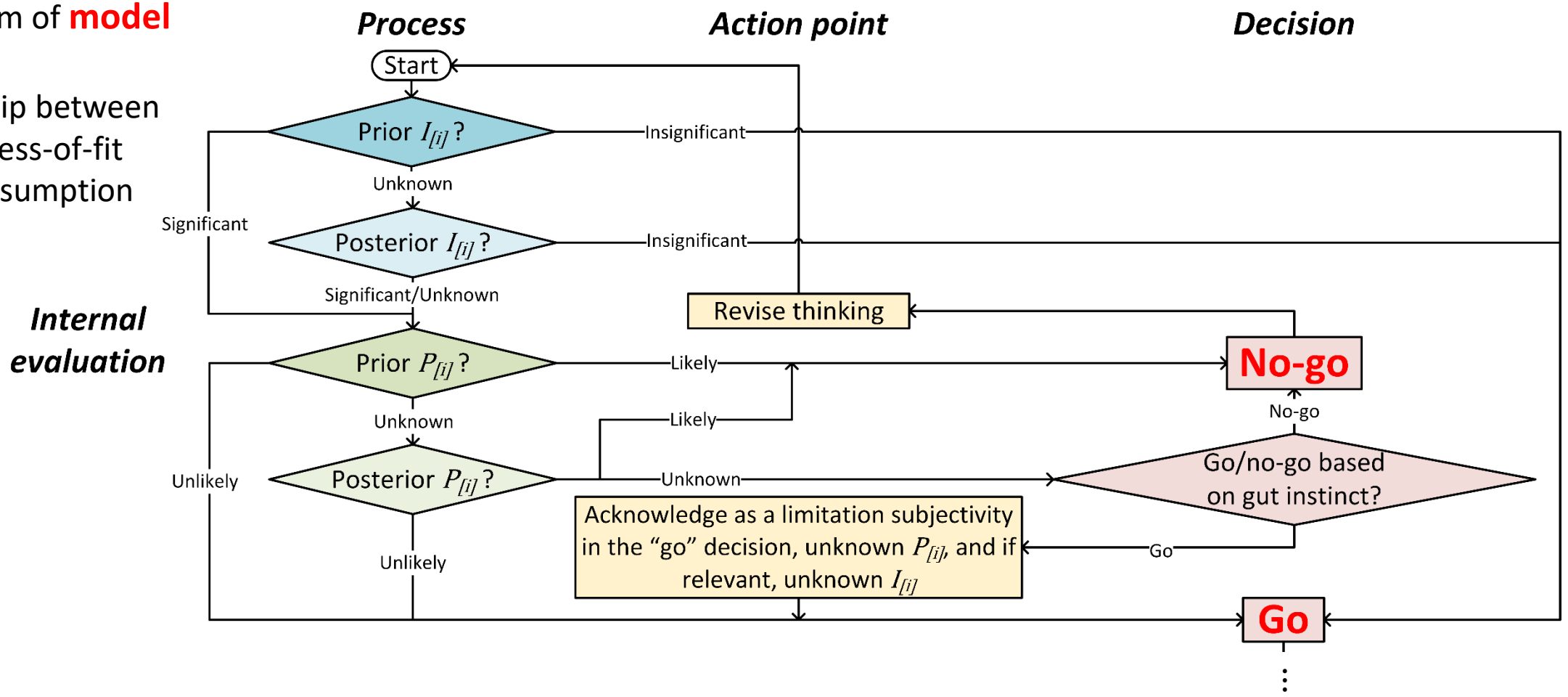
End

Internal evaluation

Internal evaluation:

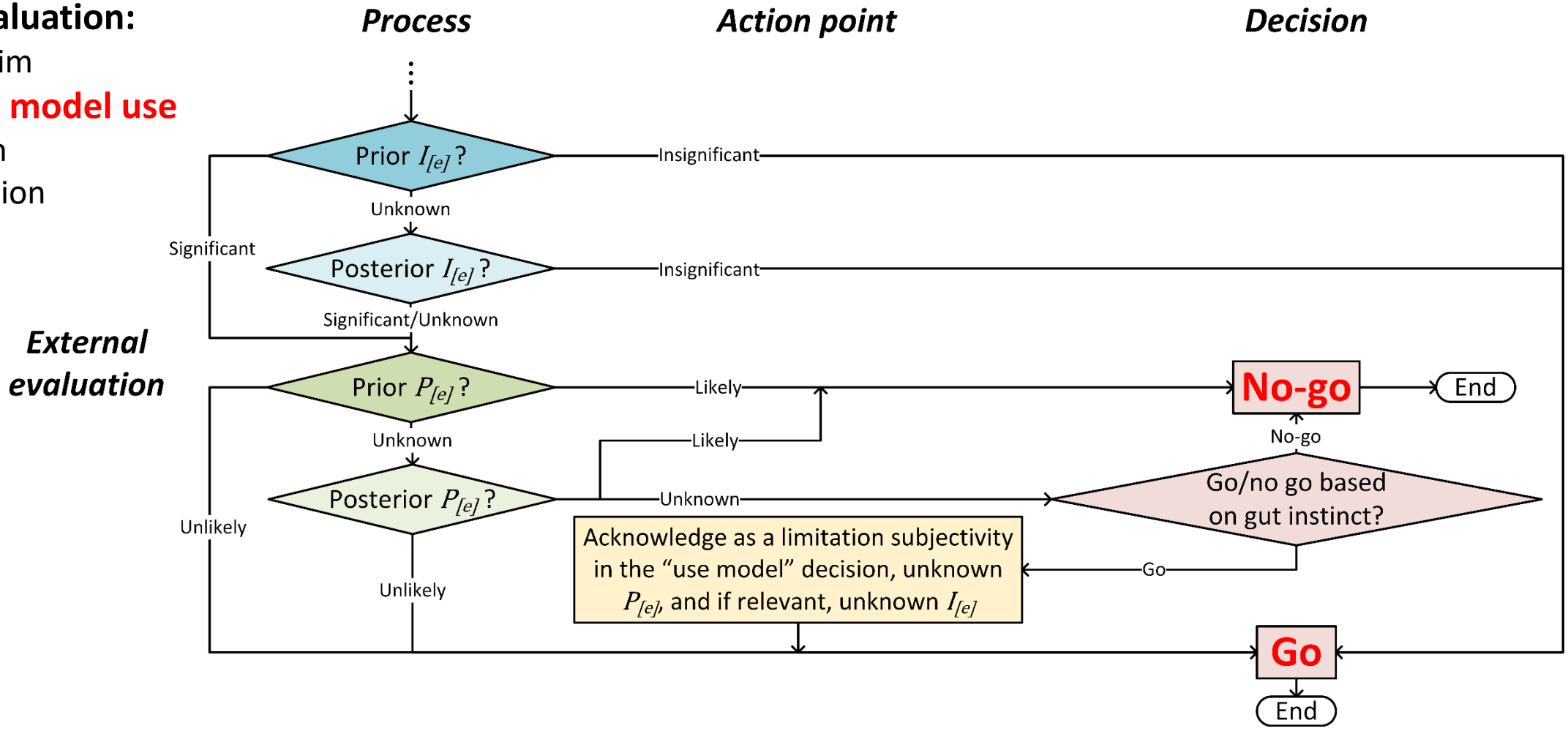
- Internal aim of **model building**
- Relationship between the goodness-of-fit and the assumption



External evaluation

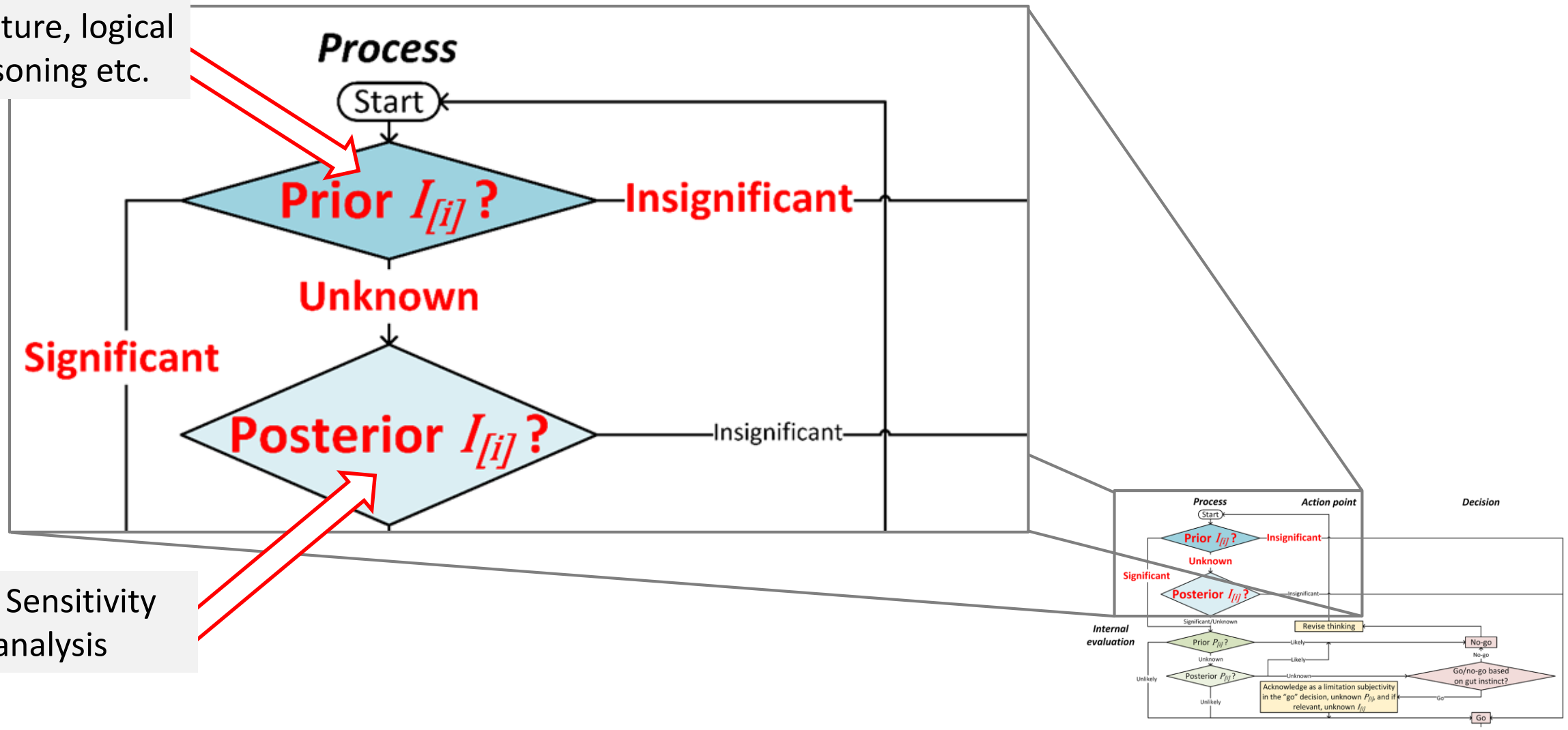
External evaluation:

- External aim
- Related to **model use**
- Simulation
- Extrapolation



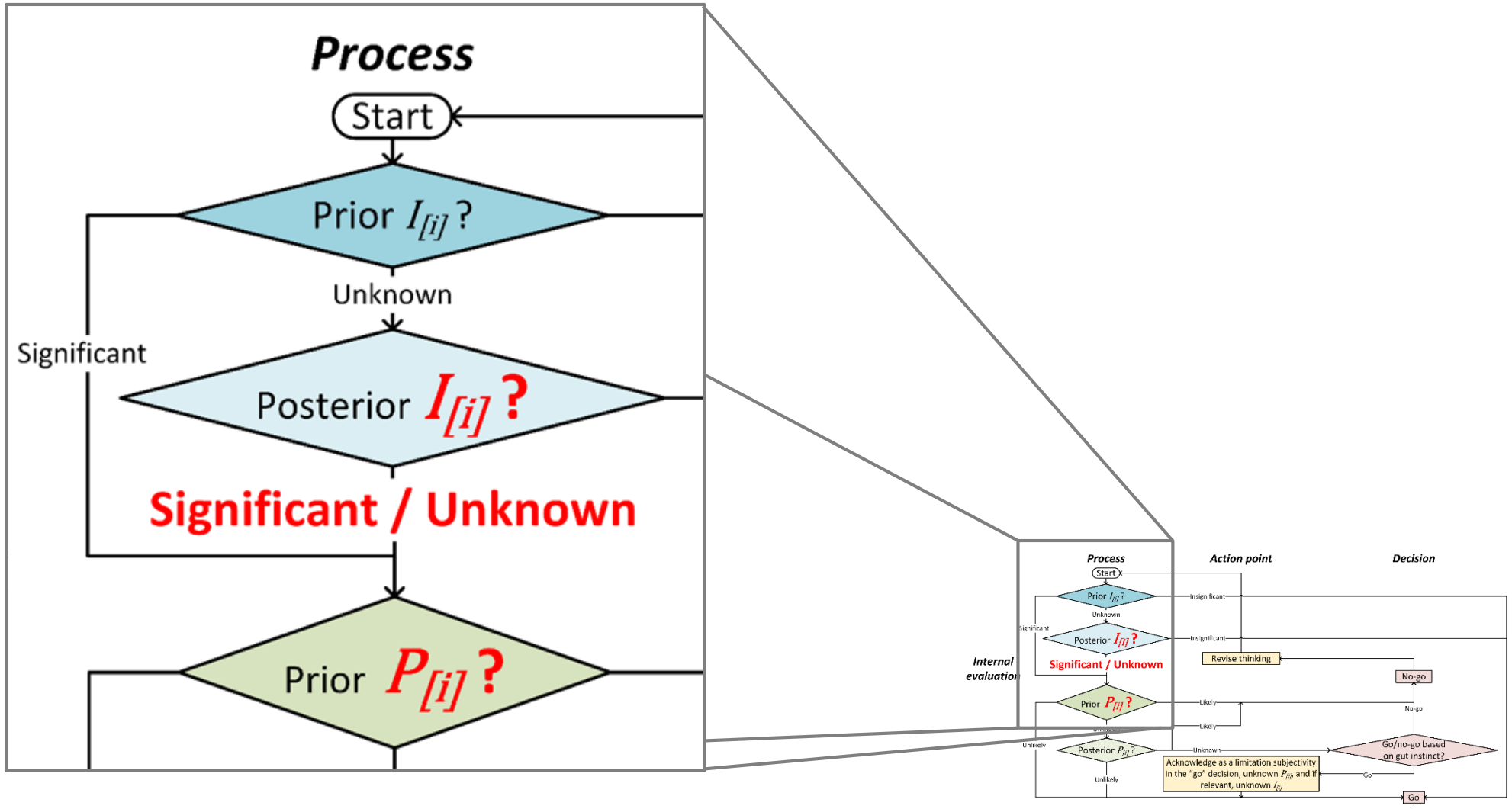
Impact of assumption violation, I

Literature, logical reasoning etc.



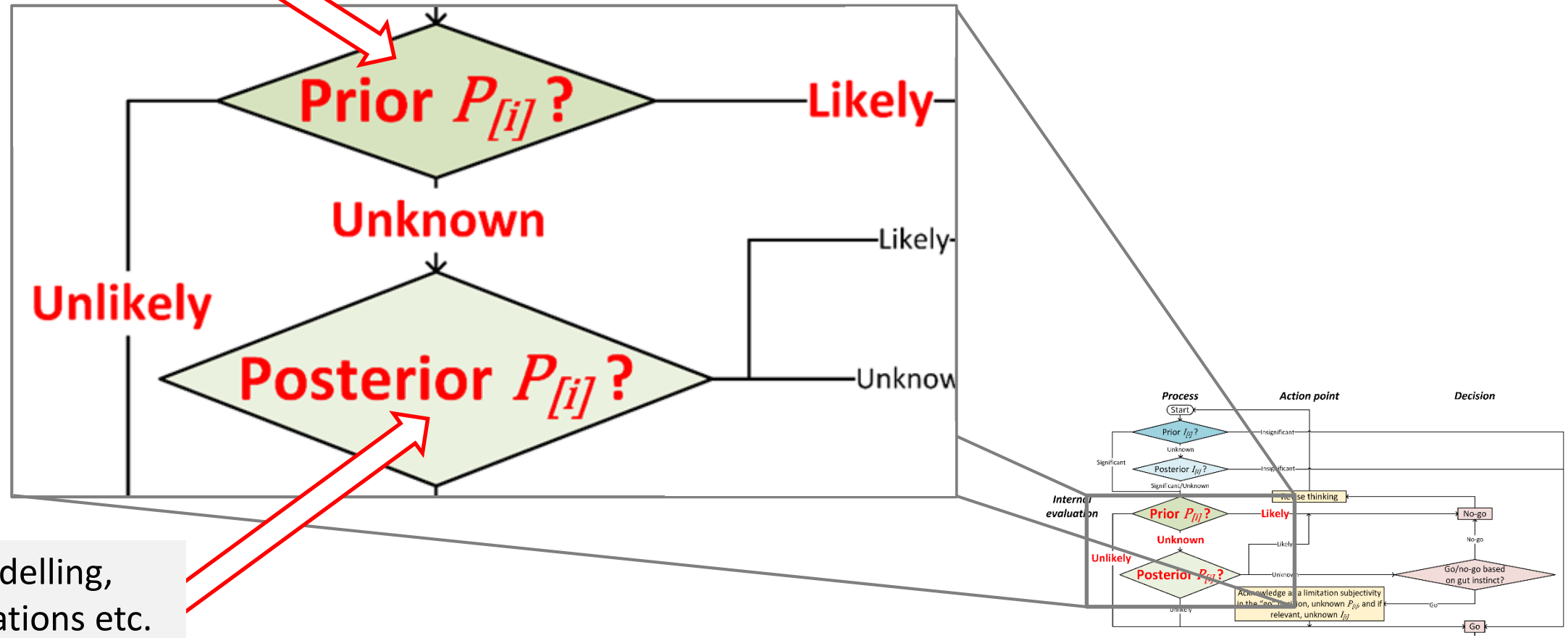
e.g. Sensitivity analysis

Risk stratification based on I



Probability of assumption violation, P

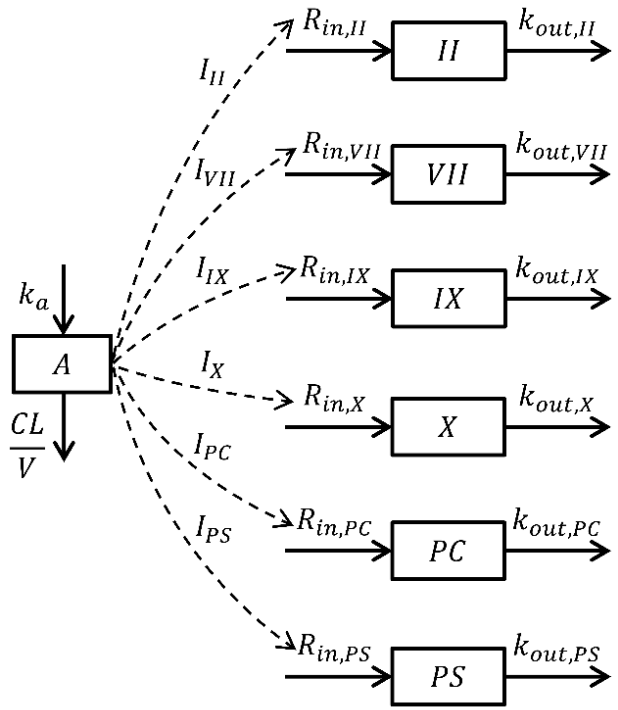
Literature, logical reasoning etc.



Modelling, simulations etc.

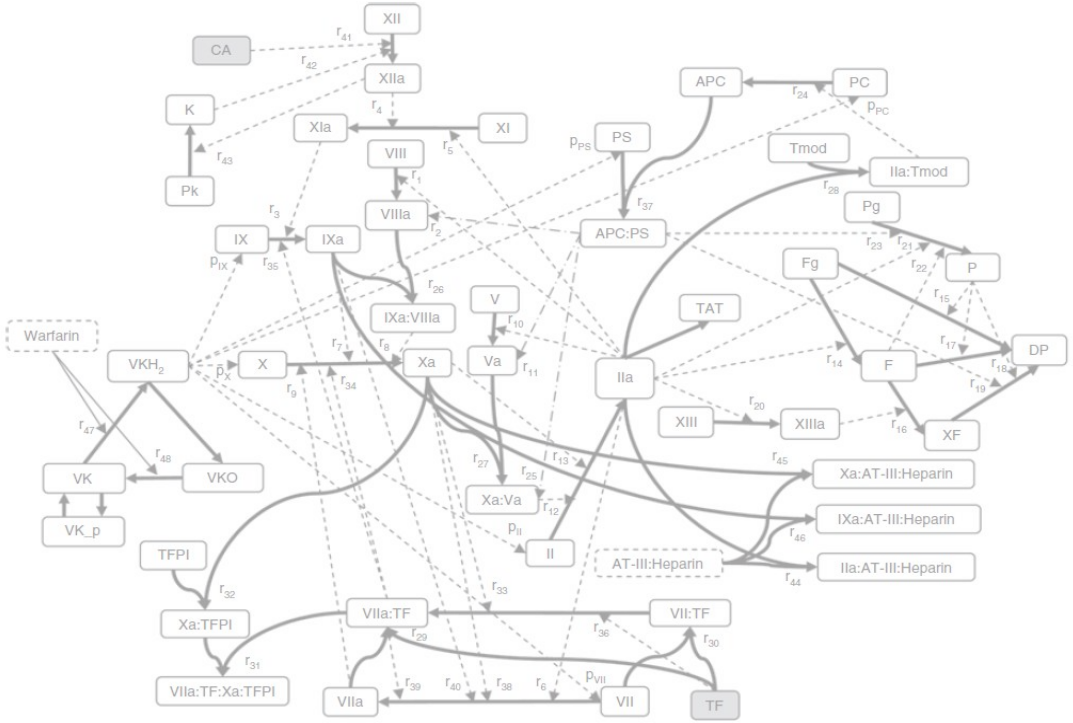
Application

- 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

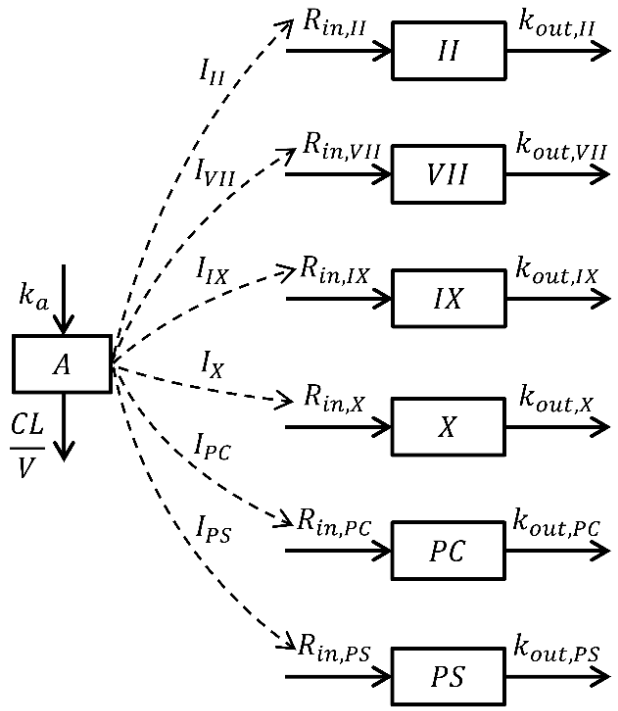
- Bottom-up example
  - Factor VII-based method for INR prediction based on a QSP coagulation network model



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

Demonstration of the utility of the flowchart

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



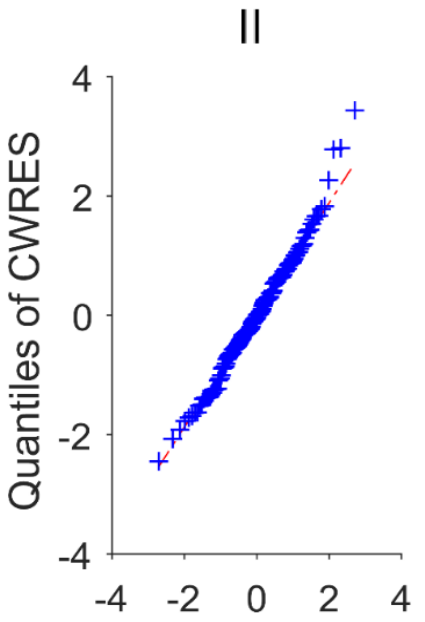
Ooi et al., Clin Pharmacokinet. 2017; 56(12):1555-66

1. **Internal** evaluation of **implicit** assumption
2. **Internal** evaluation of **explicit** assumption
3. **External** evaluation of **implicit** assumption
4. **External** evaluation of **explicit** assumption

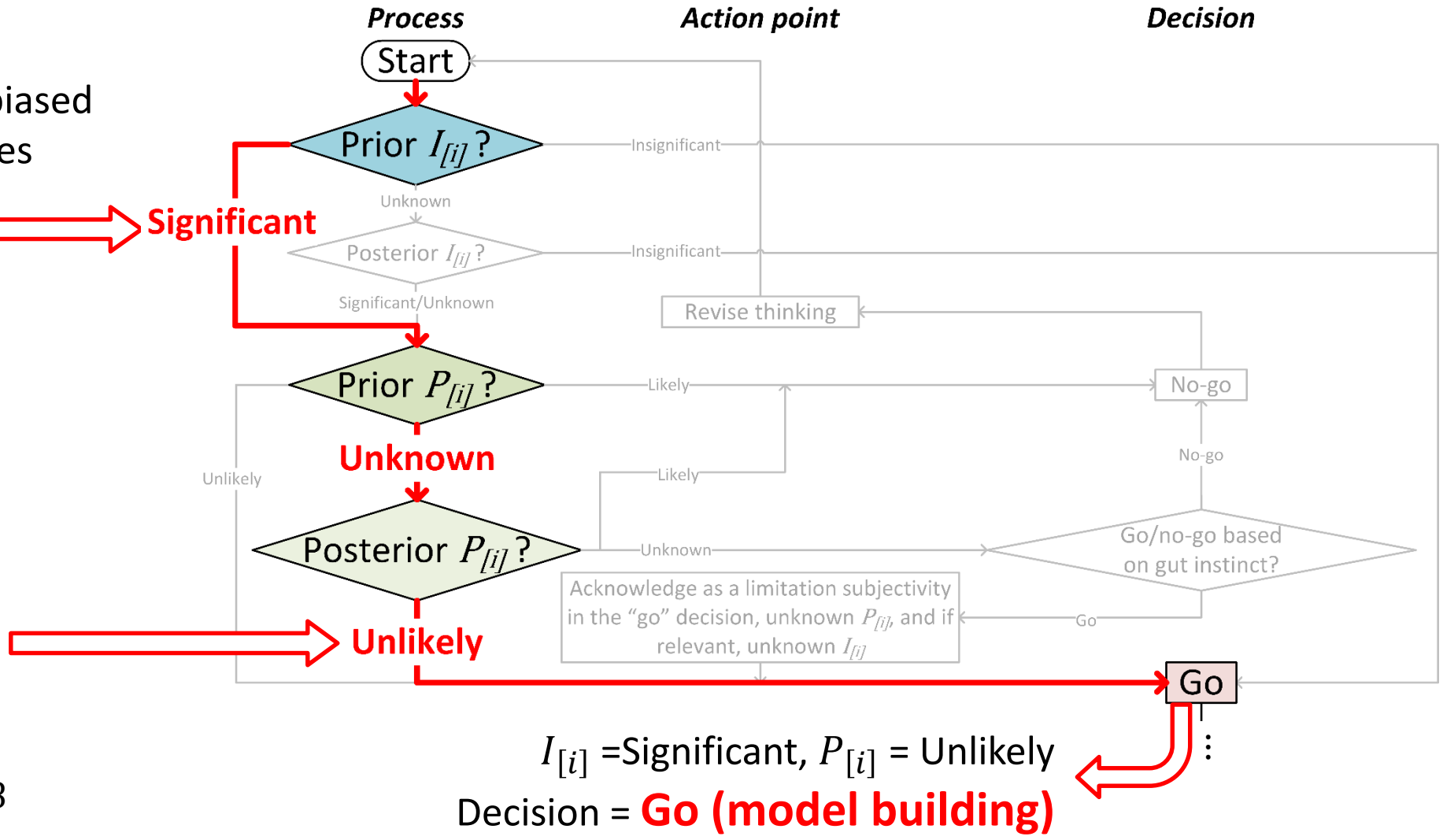
1. Internal evaluation of implicit assumption: $\varepsilon \sim N(0, \sigma^2)$

Prior knowledge:

Non-normality → biased parameter estimates



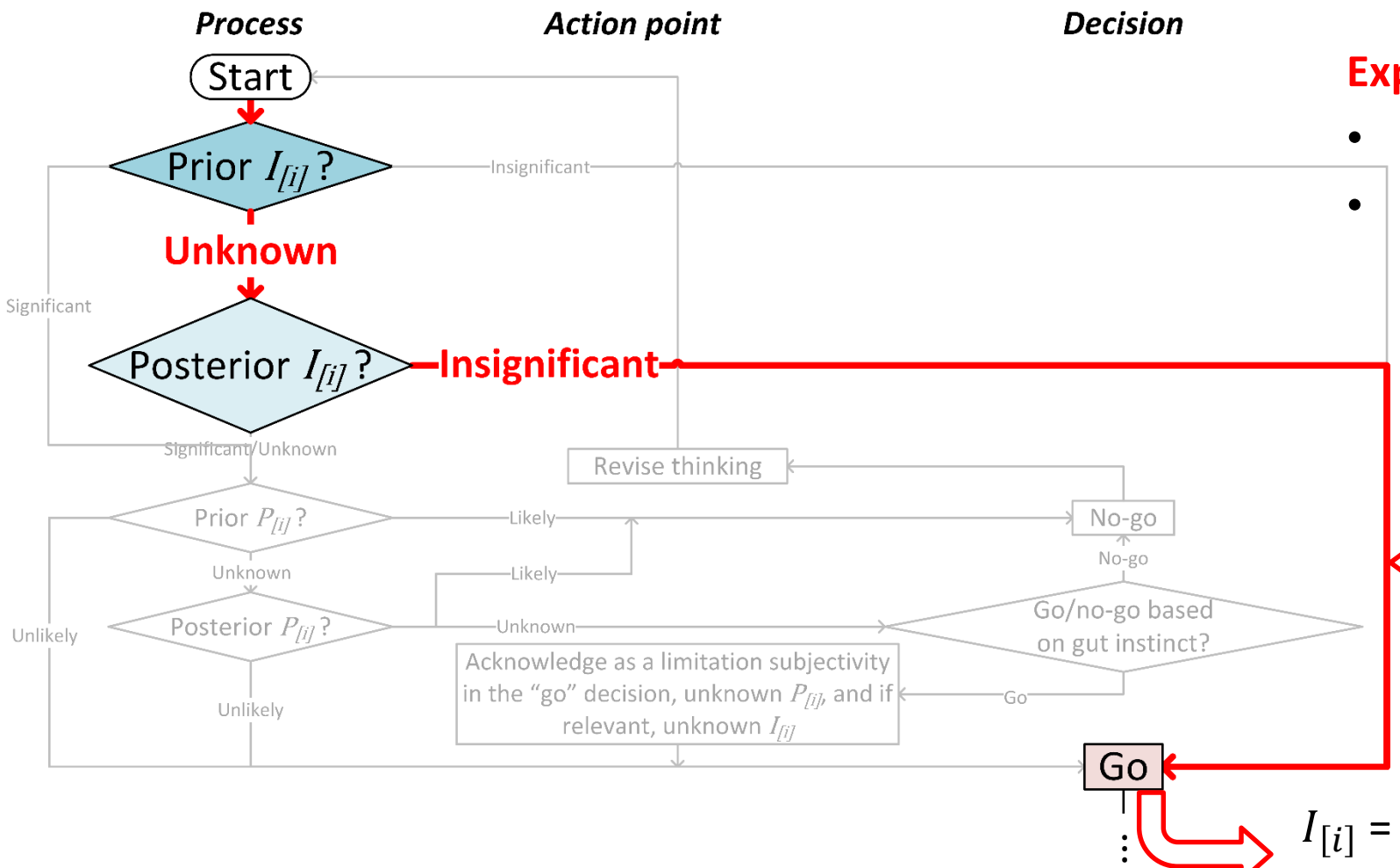
KS test: $p = 0.998$



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

Decision = **Go (model building)**

2. Internal evaluation of explicit assumption: Daily dose time of 6pm



Explicit assumption:

- Actual daily dose time not recorded
- Based on study protocol → **imputation**

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

$I_{[i]}$ = Insignificant

Decision = **Go (model building)**

3. External evaluation of implicit assumption: Reversible binding

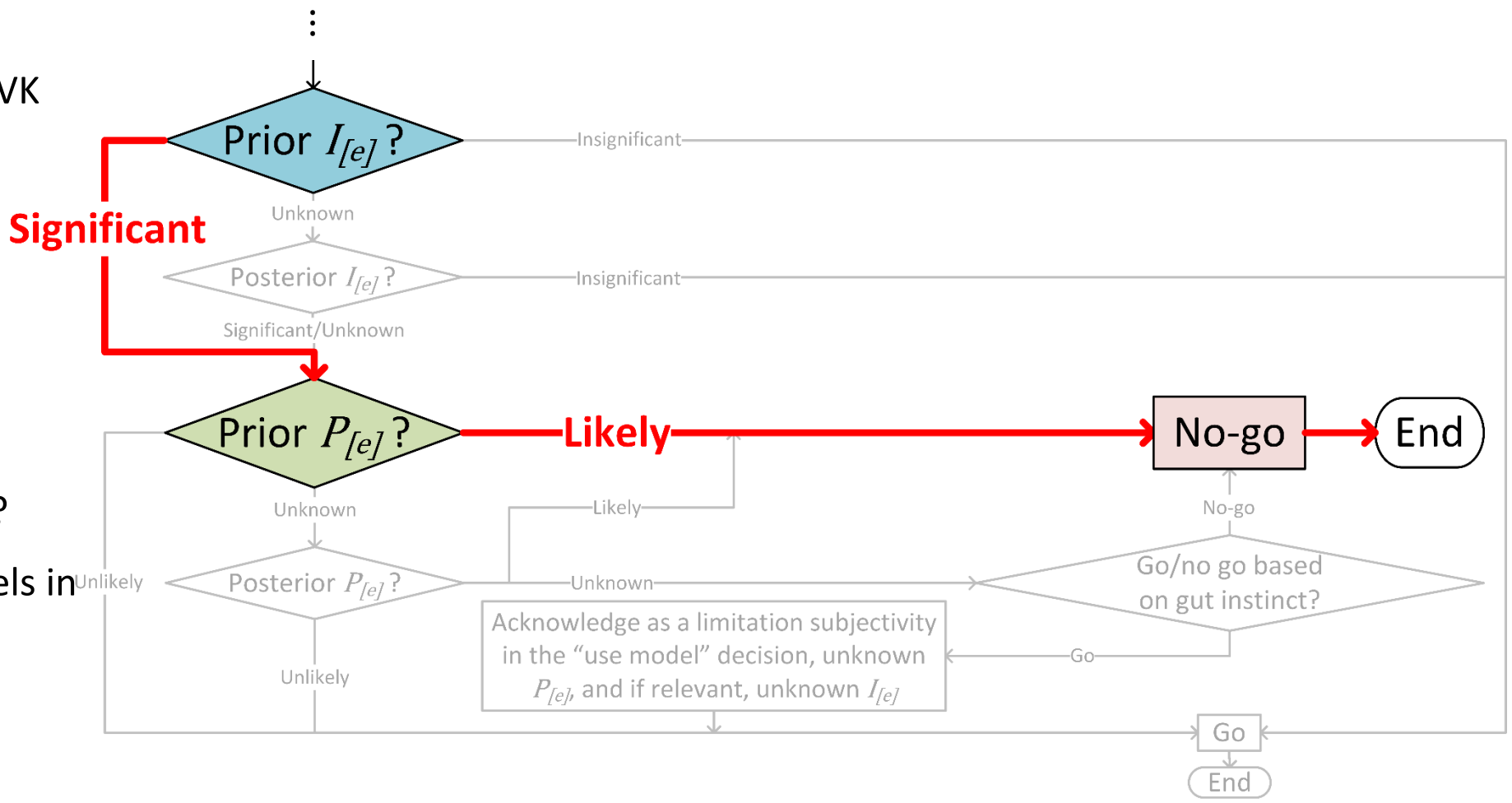
E_{max} model:

- Binding of warfarin and VK to VKOR → reversible
- Constant VK

External evaluation:

- How to evaluate an assumption against an **external aim** of interest?
- To predict the factor levels in **different population**

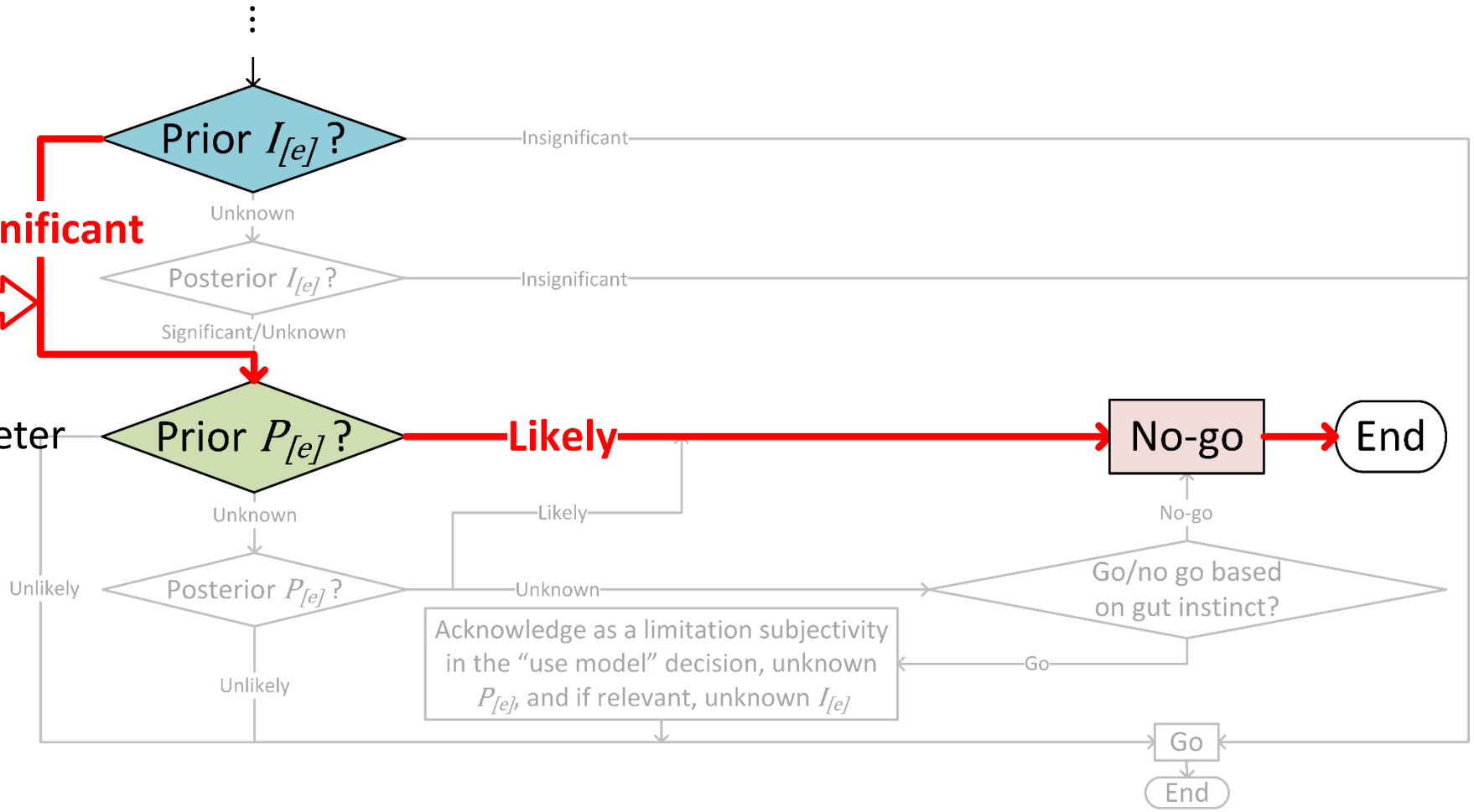
  e.g. VK supplementation



3. External evaluation of implicit assumption: Reversible binding

Sensitivity analysis:

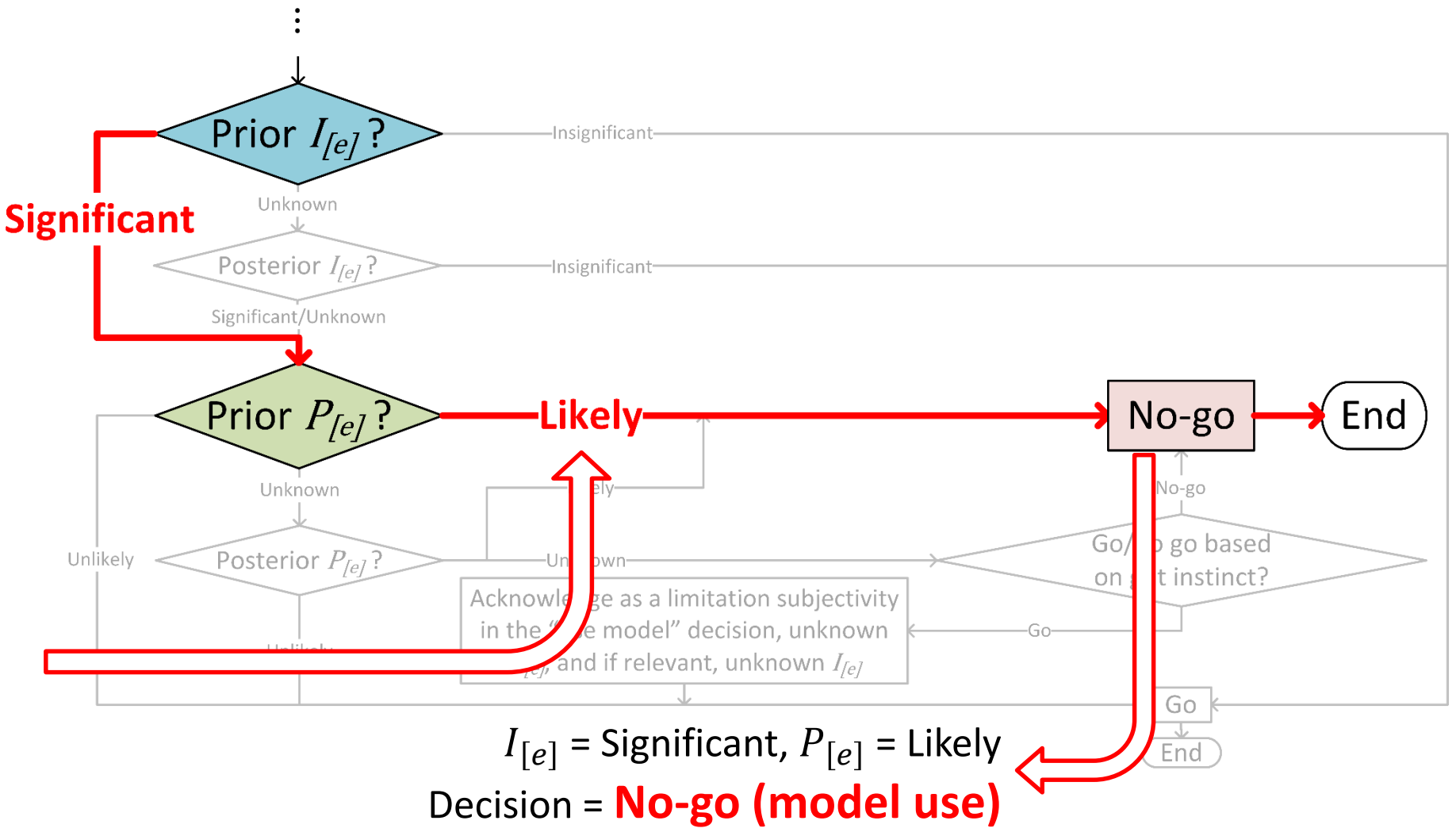
- Deviation from reversible binding or different parameter estimates (e.g. A_{50})
- Different predictions



3. External evaluation of implicit assumption: Reversible binding

Prior knowledge:

- VK supplementation
- Variable A_{50} i.e. $A_{50}(t)$
- Extrapolation to new population → biased predictions



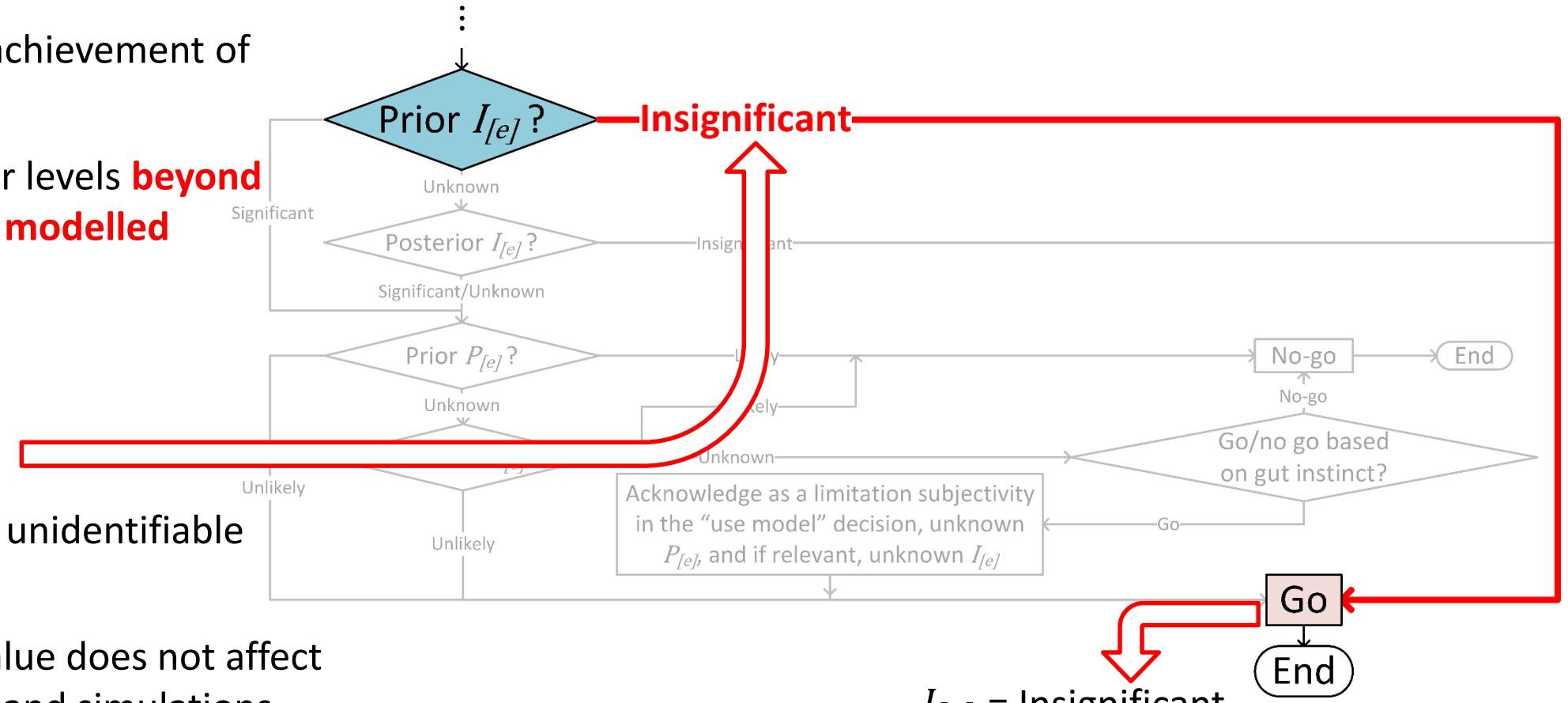
4. External evaluation of explicit assumption: $V = 8\ L$

External evaluation:

- Impact on the achievement of **external aim**
- To predict factor levels **beyond the dose range modelled**

Prior knowledge:

- V is structurally unidentifiable without PK data
- The assumed value does not affect K-PD model fits and simulations



$I_{[e]}$ = Insignificant

Decision = **Go (model use)**

Suggested assumption table

- Documentation of assumptions → EFPIA's white paper on good practices in MID3
- Adapted and expanded for use in concert with the flowchart

Assumption	Impact (I)			Probability (P)			Decision
	Methods	Results	Rating	Methods	Results	Rating	
State the assumption	Prior or posterior? Testable? Outline method	Summarise results and justify rating	Significant / insignificant / unknown	Prior or posterior? Testable? Outline method	Summarise results and justify rating	Likely / unlikely / unknown	Go or no-go for model building or model use

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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
  - A web-based application / package in a software can be introduced to help modellers to evaluate assumptions comprehensively and efficiently

Acknowledgements

- University of Otago Doctoral Scholarship
- School of Pharmacy, University of Otago
- Otago Pharmacometrics Group
- Clinical Research Centre, Ministry of Health Malaysia