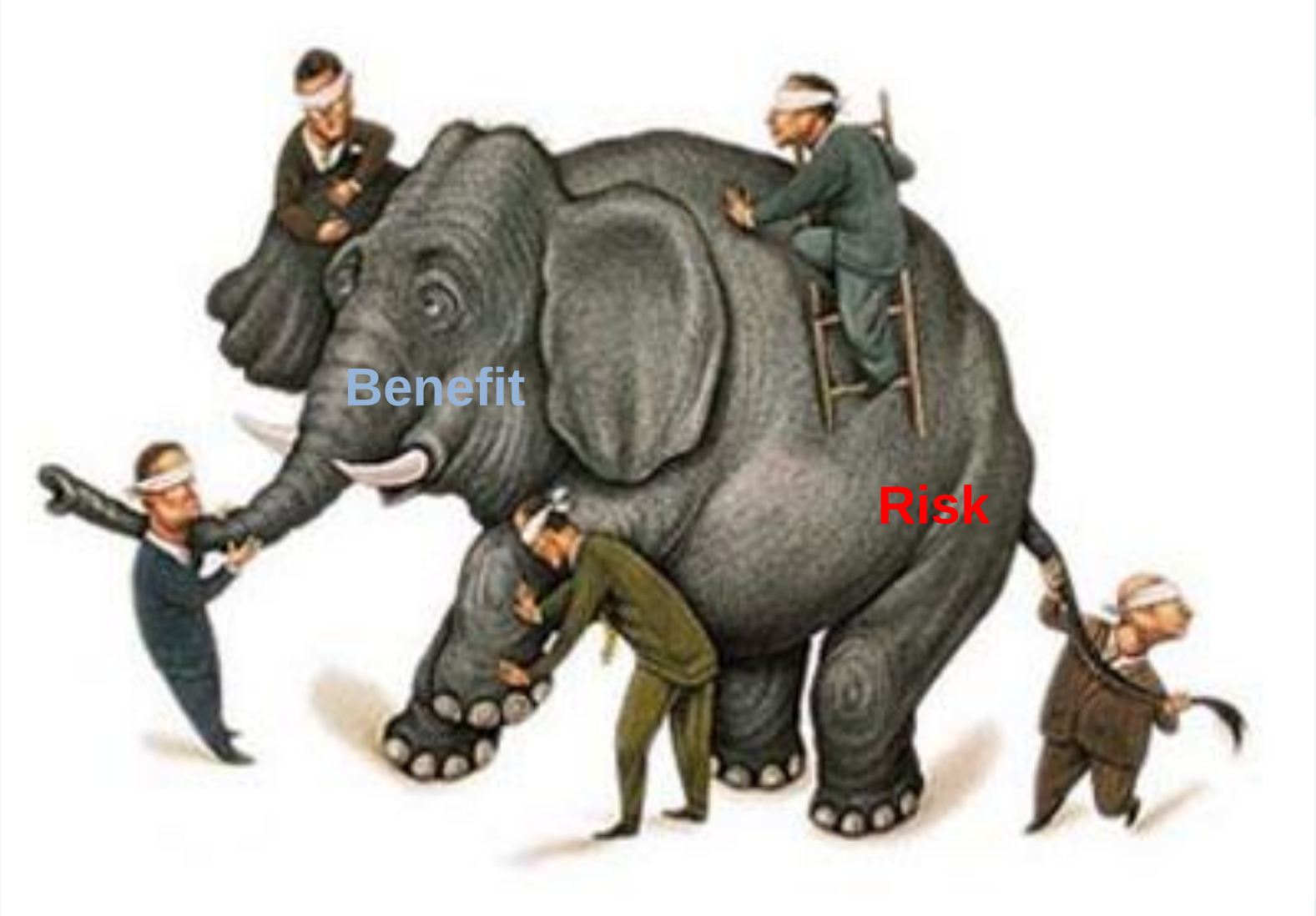
Quantitative benefit-risk assessment: An analytical framework for a shared understanding of the effects of medicines

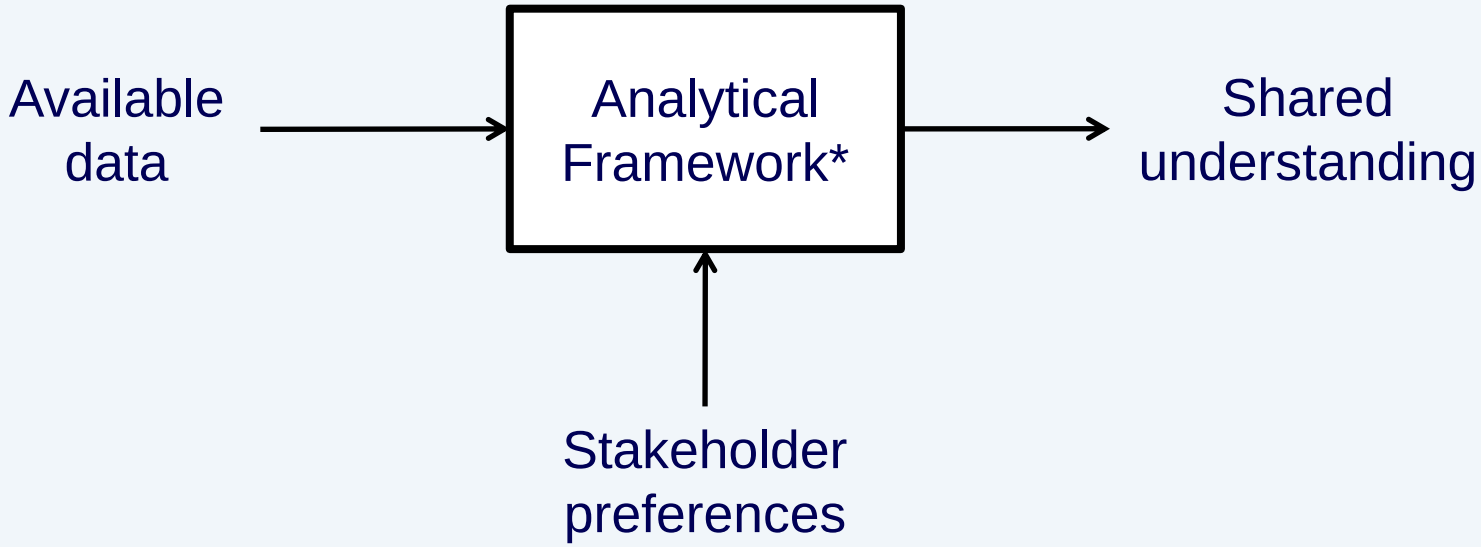
Patrick Ryan

21 April 2010

Challenges in understanding the effects of medicines



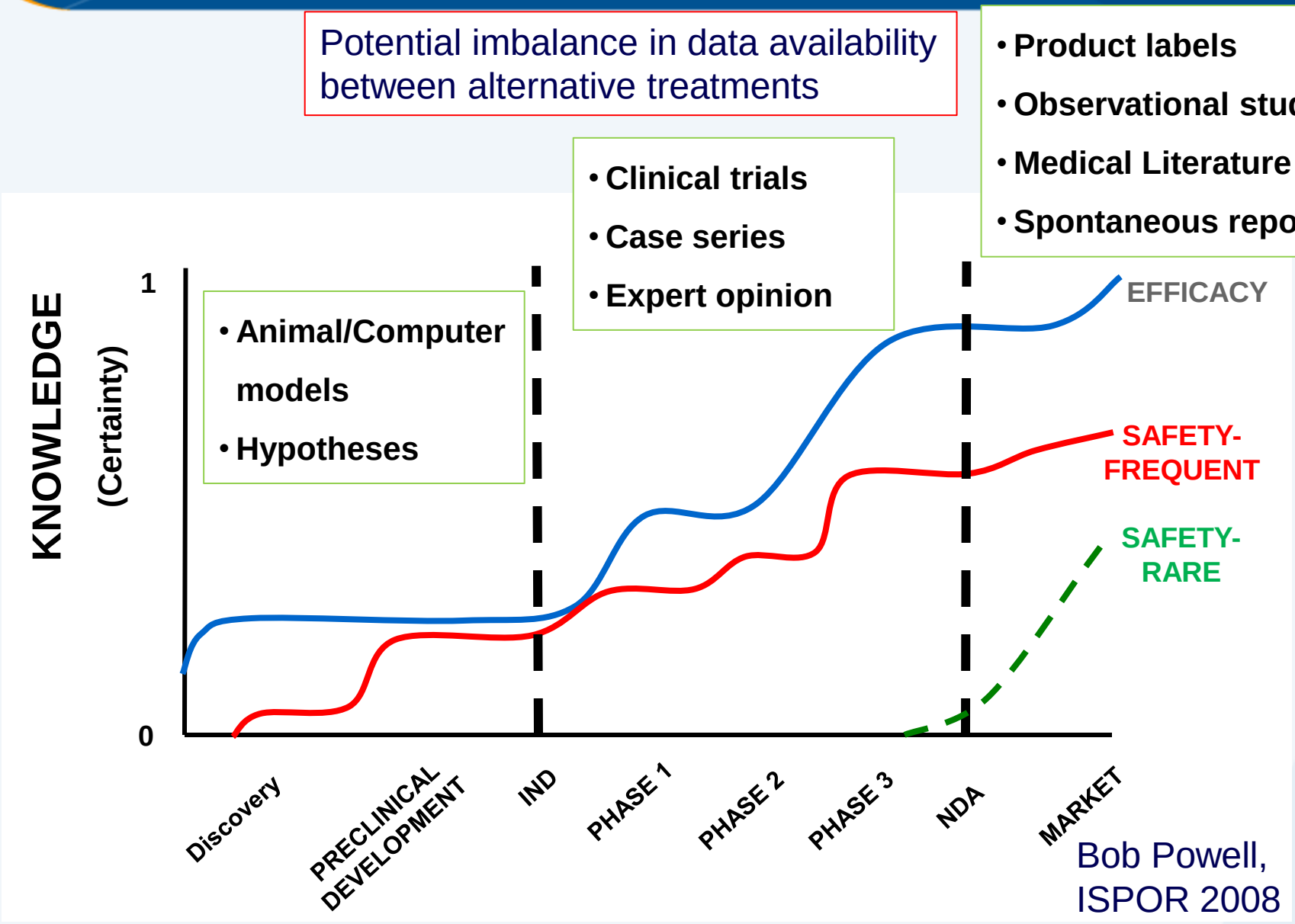
Benefit-risk analysis process



*tailored to the complexity of the decision

Diversity of data availability

Potential imbalance in data availability between alternative treatments



Bob Powell, ISPOR 2008

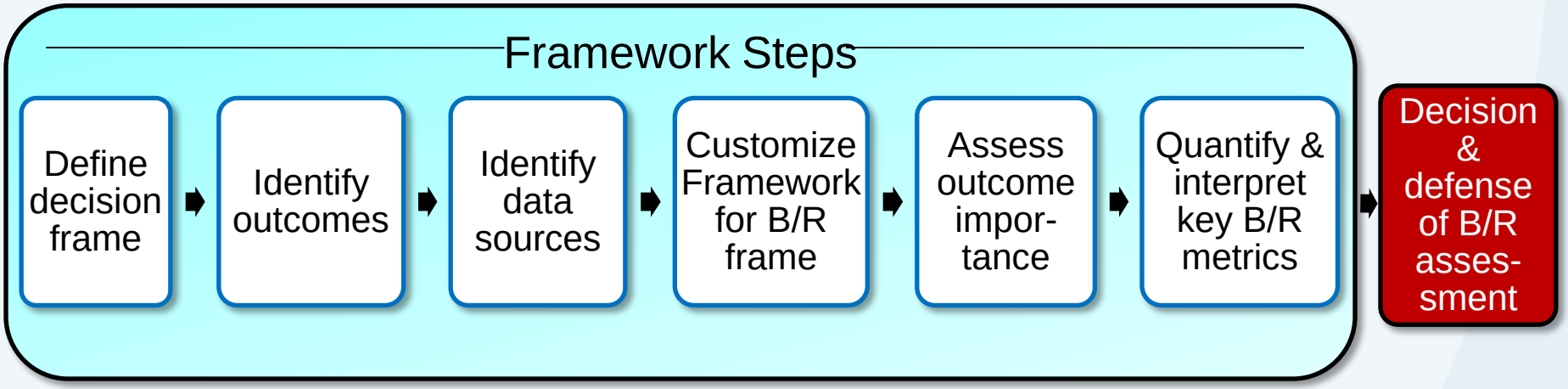
Components of an analysis framework

- Define decision
- Identify health outcomes
- Synthesize data
- Model decision and conduct analysis
- Interpret and evaluate results

PhRMA Benefit Risk Action Team (BRAT) Framework

- A set of principles, processes and tools to guide decision-makers in
  - Selecting
  - Organizing
  - Understanding
  - Summarizing

  Evidence relevant to benefit-risk decisions



Levitan and Andrews, "Example Application of PhRMA BRAT (Benefit-Risk Action Team) Framework", Assessing Benefits and Risks of Medicinal Products in Regulatory Decisions, DIA, Nov, 2009

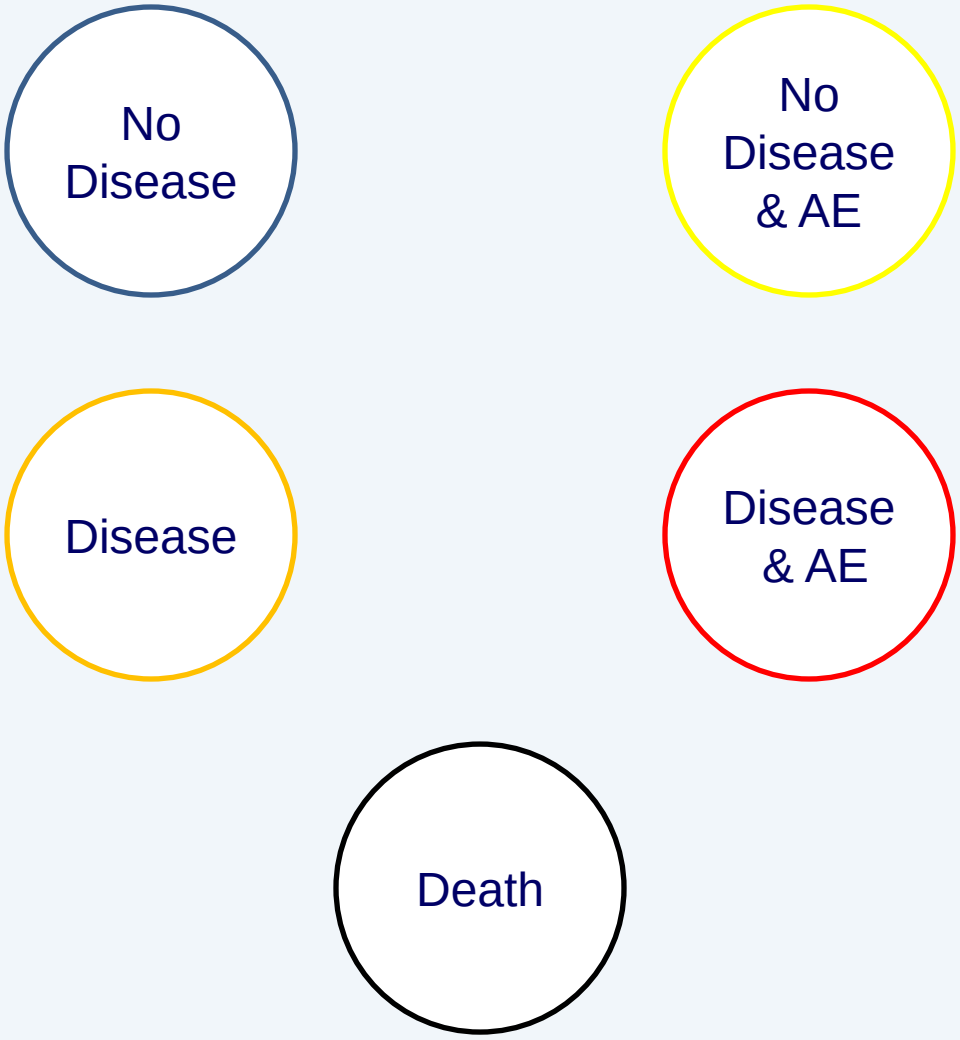
Define decision

- Multiple stakeholders face decisions throughout the medical product lifecycle:

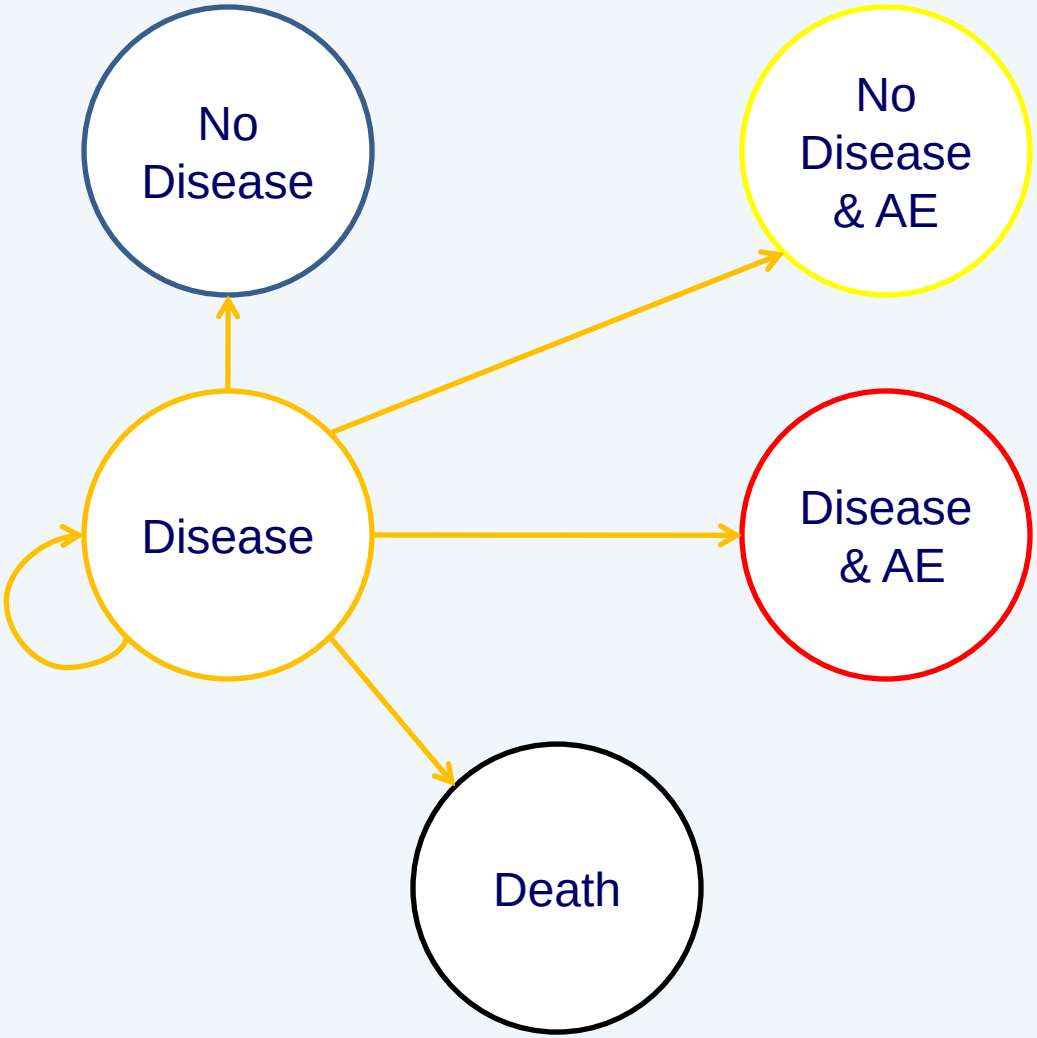
  Industry : **Do we continue investing?**
  Regulatory: **Do we approve?**
  Payer: **Do we reimburse?**
  Provider: **Is this best for my patients?**
  Patient: **Is this the best drug for me?**

- Analysis needs to be flexible to accommodate diverse perspectives to inform stakeholder decision-making processes

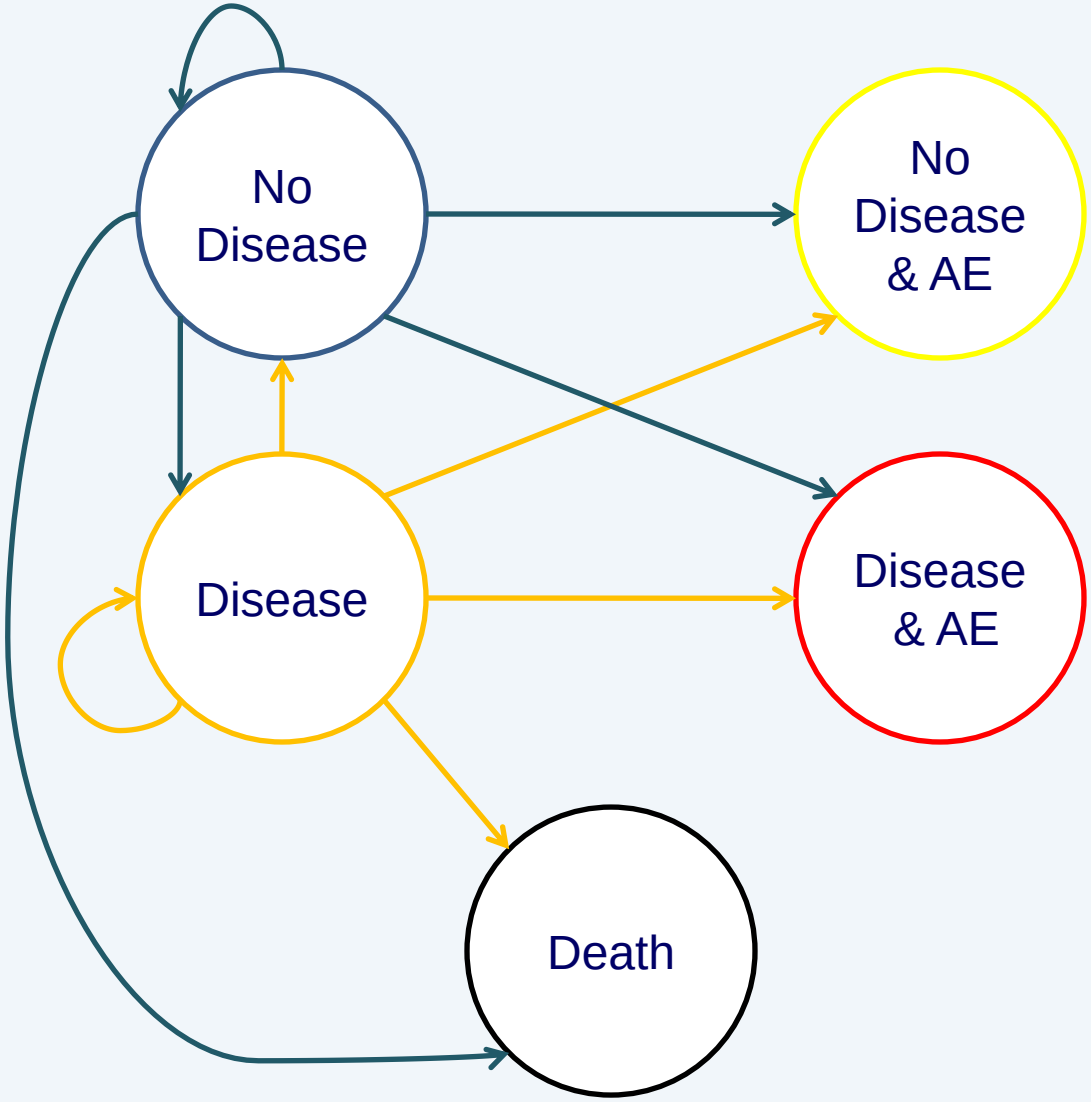
Illustrative example:
Identify health outcomes



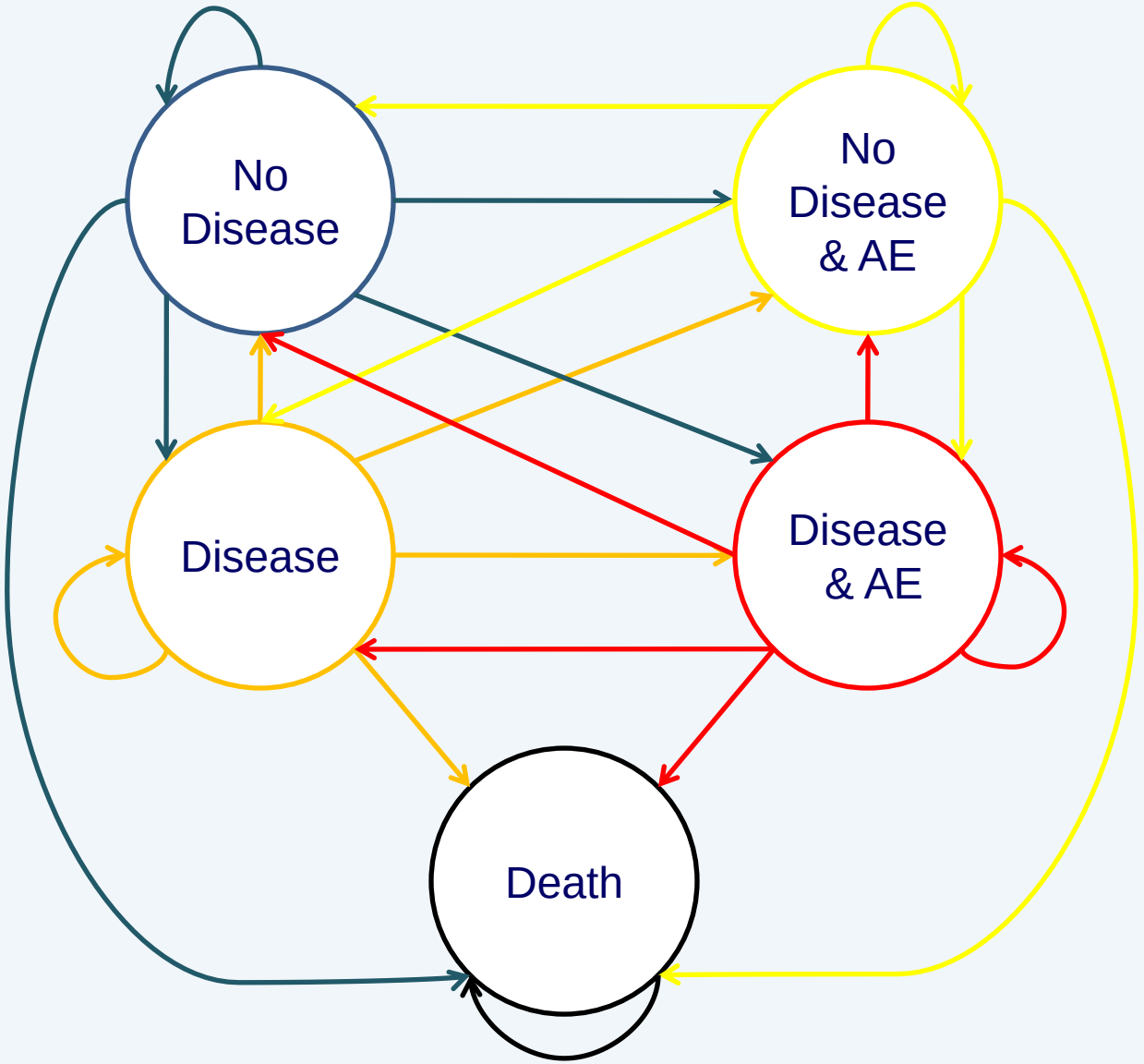
Illustrative example:
Transitions between health states



Illustrative example:
Transitions between health states

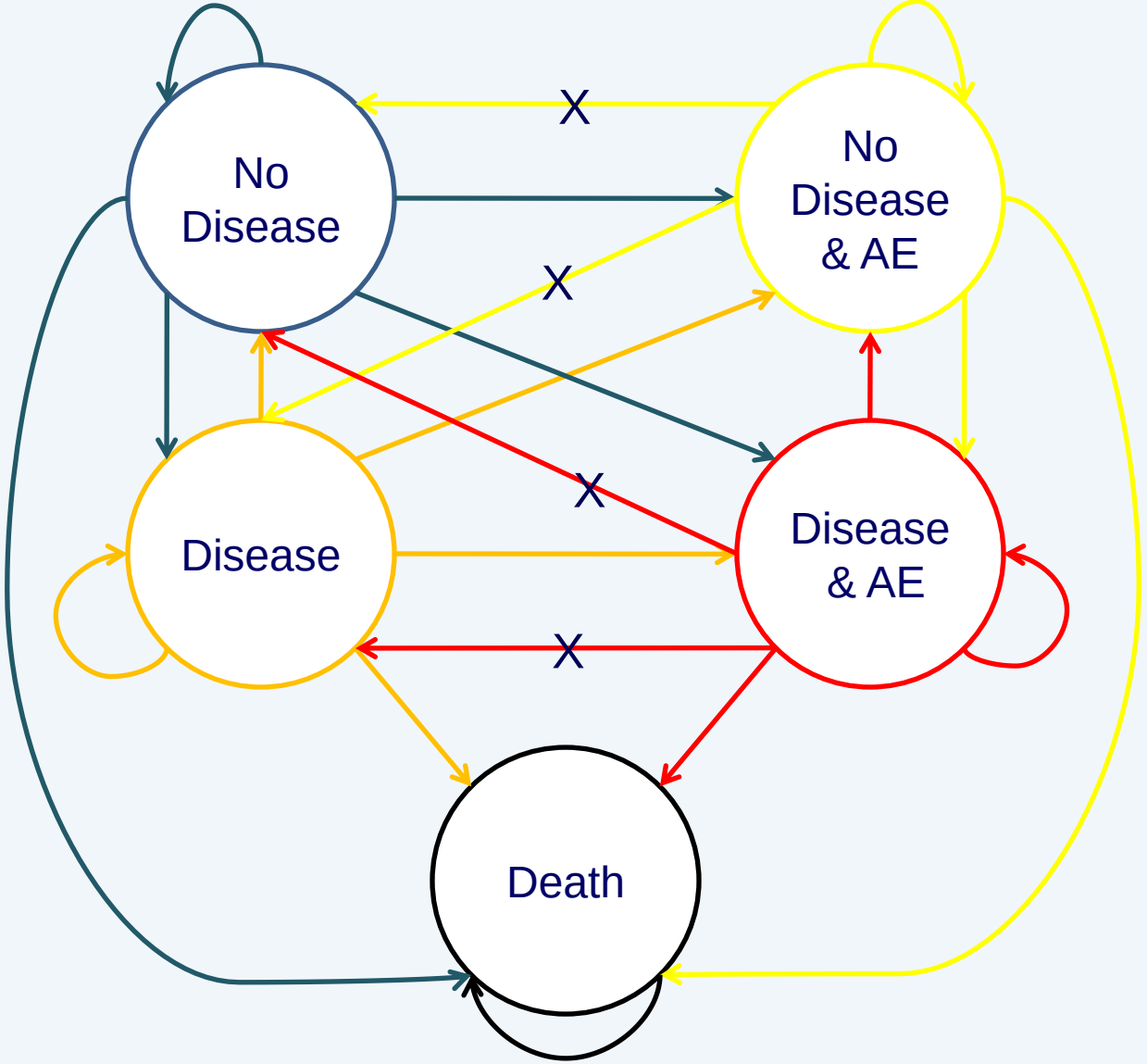


Illustrative example:
Building a full model

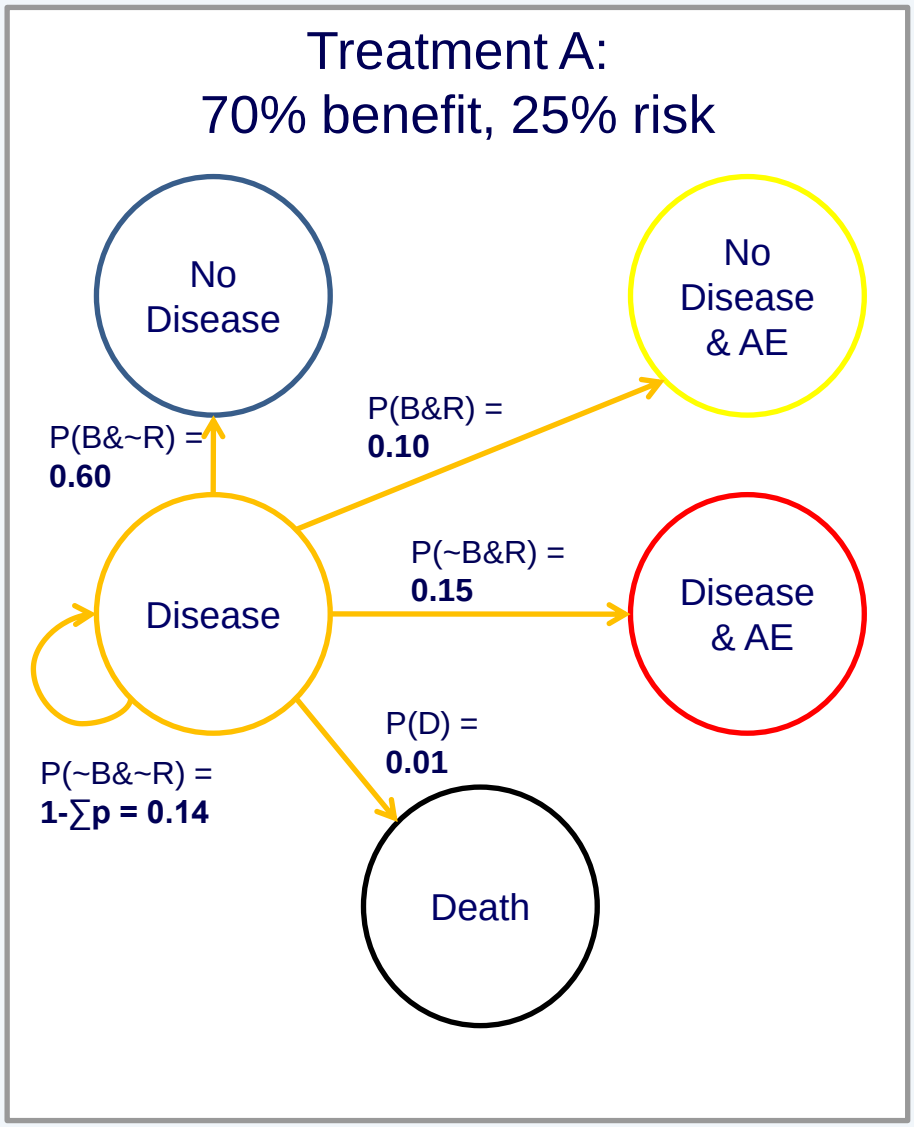


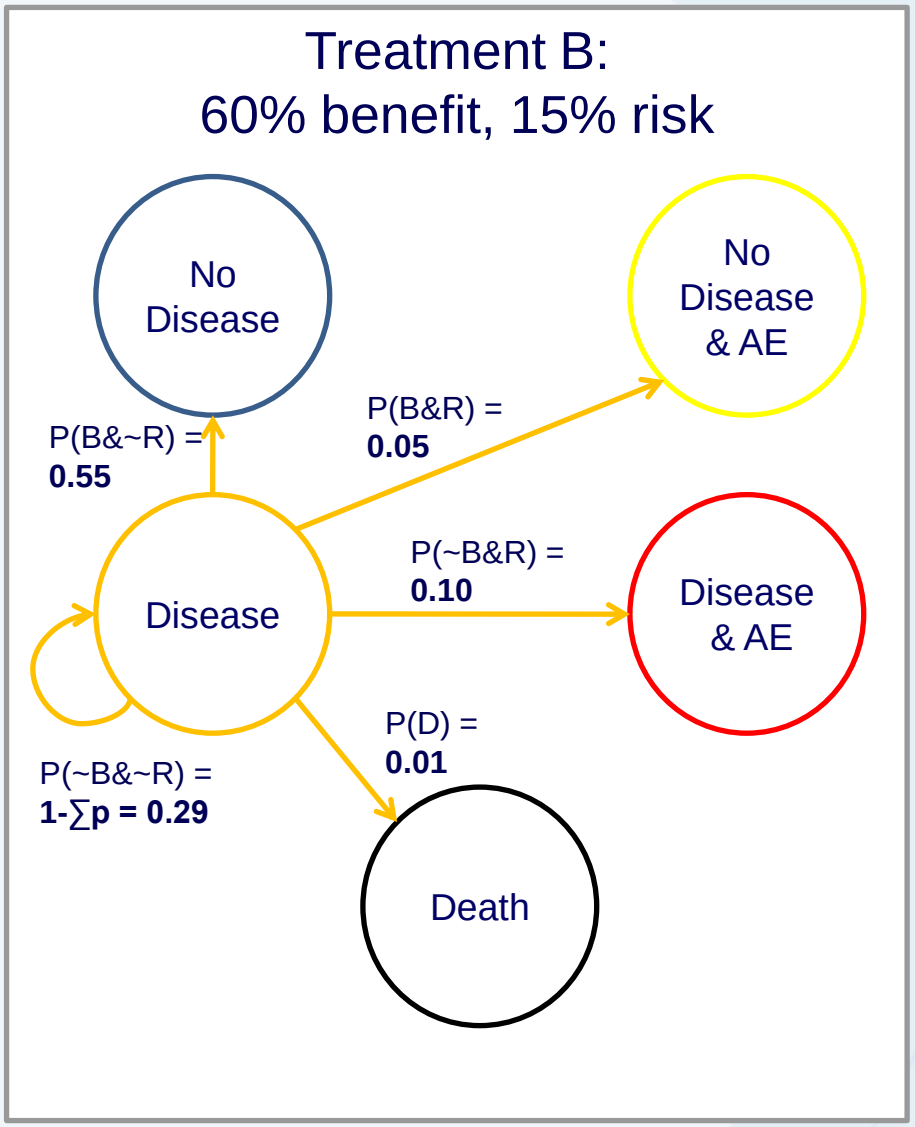
Illustrative example:
Modeling meets data challenges

What if there are no data available to characterize adverse event resolution?



Comparing alternative treatments





Potential tradeoffs in a benefit-risk analysis

- **Competing risks**
  Ex: rofecoxib vs. NSAID: GI bleed vs. acute myocardial infarction
- **Competing benefits**
  Ex: RA: inflammation pain relief vs. QoL measures
- **Higher benefit and higher risk**
  Ex: natalizumab : MS treatment vs. PML
- **Outcomes occurring at different times**
  Ex: chemotherapy: immediate nausea, alopecia vs. long-term survival
- **Varying uncertainty**
  Ex: Typical vs. atypical antipsychotics

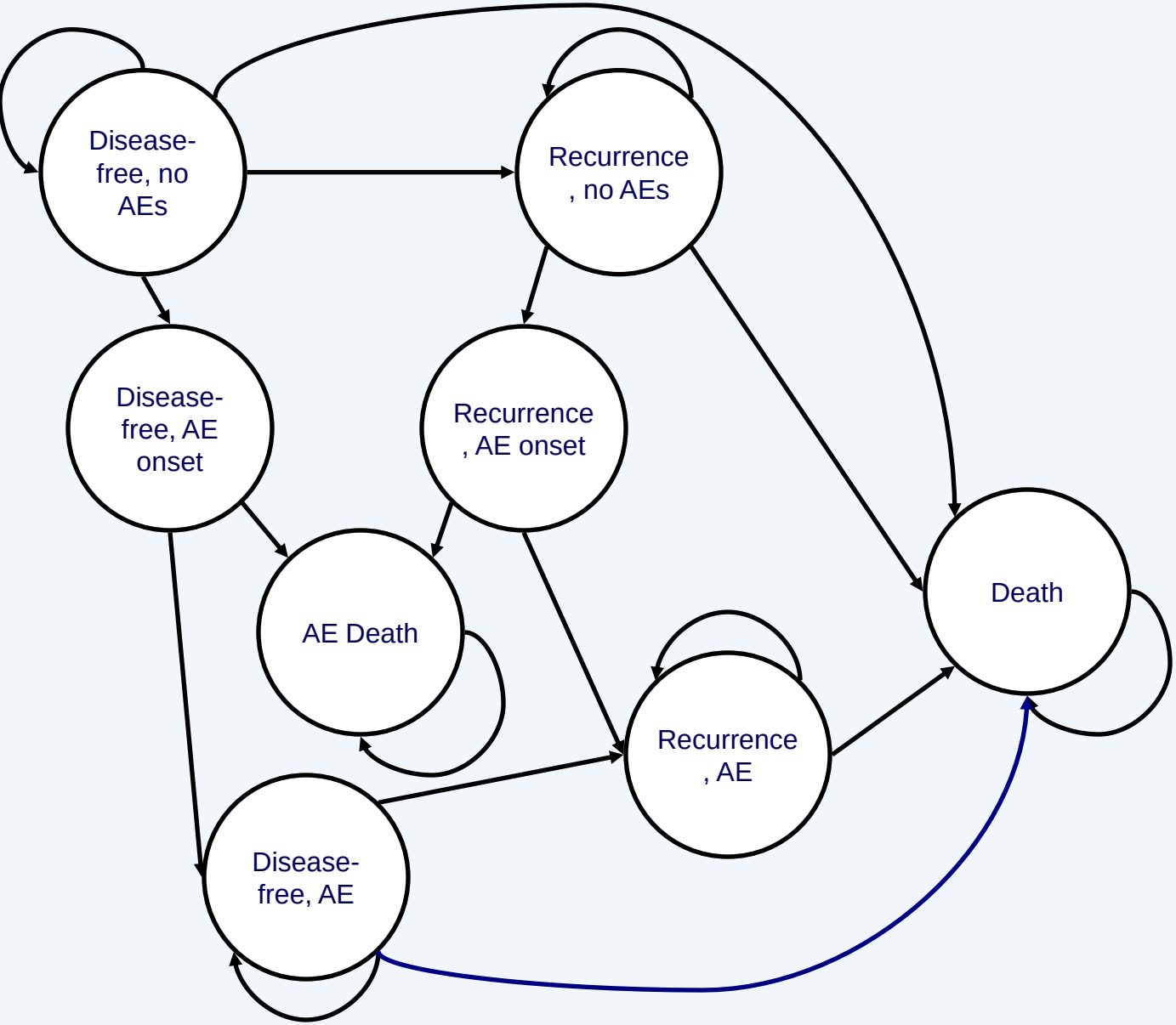
Any or all of these tradeoffs can play out in a given decision:

Multiple competing benefits with multiple competing risks over time

Translating concept into practice

Ideal scenario	Real scenario
Each drug has one dose……	Multiple dose regimens
Patient data for both drugs……	Aggregate summaries from literature
Clear choice of B&Hs…….	Single AEs or ‘Any Grade 4’?
All B&H reported as rates……..	Mix of rates, ratios, means
Event times are equally spaced….	Event are sporadic or nonlinear
Undisputed trade-offs……..….	No preference data
Events occur independently……..	Don’t know if events are correlated
Patients have same baseline risks.	Different patient subgroups

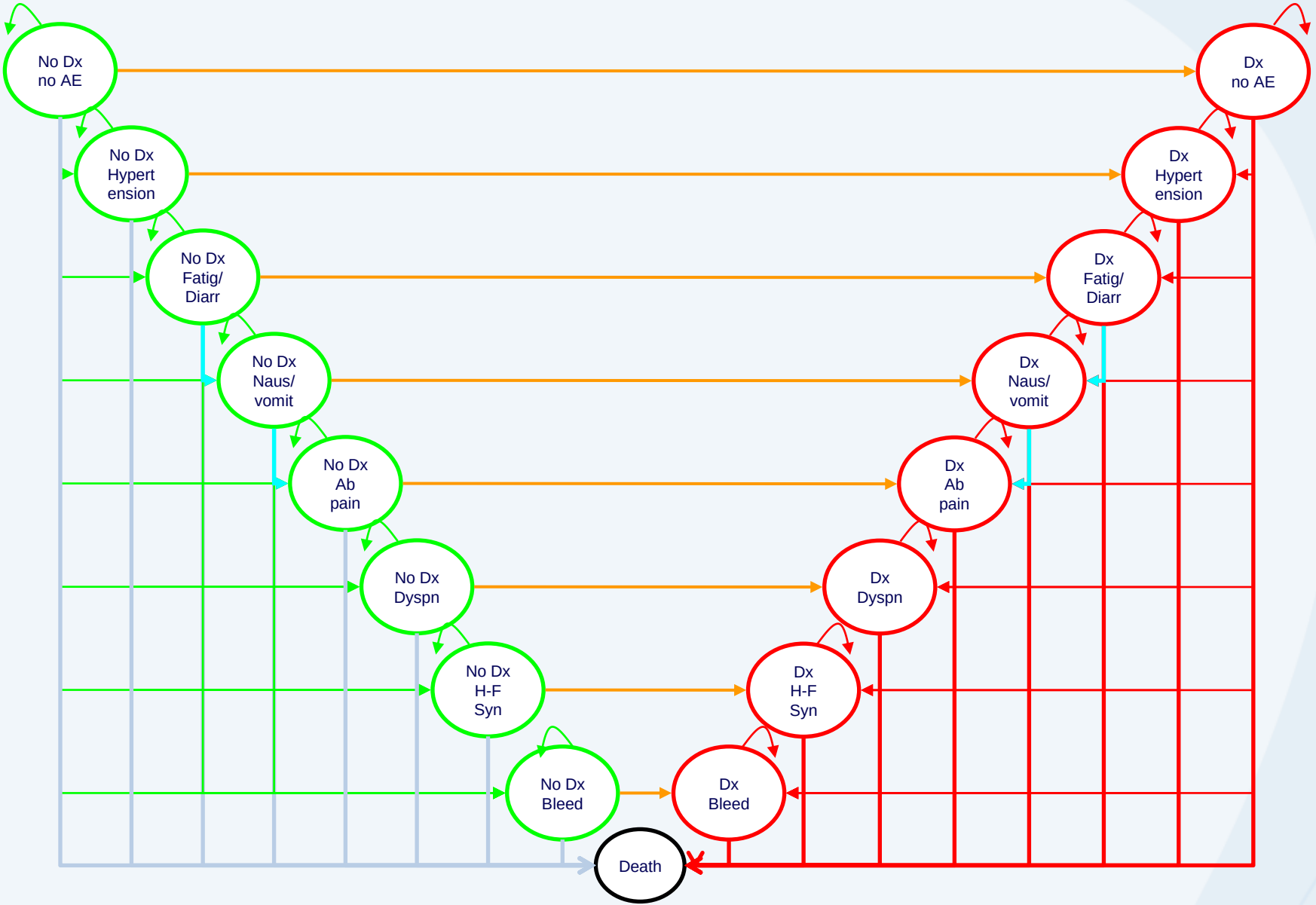
Real example: Adjuvant therapy



Assumptions:

- Treatment is 1yr, so AE rates only occur within 1 yr, then same as control.
- AE onset are tunnel states (t=0)
- AEs: Hy's Law, LVEF decreased, CHF
- Recurrence rate independent of AEs
- Hypothetical cohort of 10,000 patients for 4 years, with 1 month transition periods

Real example: Preventative Therapy



Identify Health States

Set Objective Selection Criteria:

- Clinical benefits
- Functional / QoL harms or benefits
- AEs ocurring in >x% of patients
- AEs graded x or higher
- AEs related to treatment discontinuation
- AEs with known drug class effects
- AEs that are nonreversible
- Rare AEs that received regulatory warnings

Determine which health states should be combined into a single state or split into two states.

Decide best length of time for 1 event per interval.

Synthesizing Data
ex. preventative therapy

Treatment	Placebo		Drug		Comparator		Utility	
Benefits	Value	Source	Value	Source	Value	Source	Value	Source
% Disease-free - Disease							0.8	Expert opinion
Months 0-3	1.00	RCT-301	1.00	RCT-301	1.00	JAMA 2007		
Months 3-6	0.90	RCT-301	1.00	RCT-301	1.00	JAMA 2007		
Months 6-9	0.80	RCT-301	0.95	RCT-301	0.90	JAMA 2007		
Month 9-12	0.70	RCT-301	0.90	RCT-301	0.80	JAMA 2007		
% Alive-Death							1.0	HlthAffairs 2000
Months 0-3	1.00	ISE	1.00	ISE	1.00	BMJ 2008		
Months 3-6	0.86	ISE	0.95	ISE	0.95	BMJ 2008		
Months 6-9	0.76	ISE	0.90	ISE	0.86	BMJ 2008		
Month 9-12	0.67	ISE	0.86	ISE	0.76	BMJ 2008		
Risks	Value	Source	Value	Source	Value	Source	Value	Source
Nausea	0.10	ISS	0.15	ISS	0.12	USPI	0.1	Lancet 2002
Hepatic	0.00	ISS	0.02	ISS	0.00	USPI	0.5	Hepatology 2003
Cardiac	0.00	ISS	0.00	ISS	0.03	GPRD	0.6	Heart 2007

Synthesizing Data continued

Data Limitation	→	Assumption?
Data come from ≥ 1 study		Study populations are comparable
Safety data for combined doses		Safety events are not dose-related
Safety data reported as cumulative incidence		Events occur at a constant rate
An AE is not reported for comparator		Probability is either 0 or below x%

Integrate Data into Analysis

There are many methods for integrating the data.

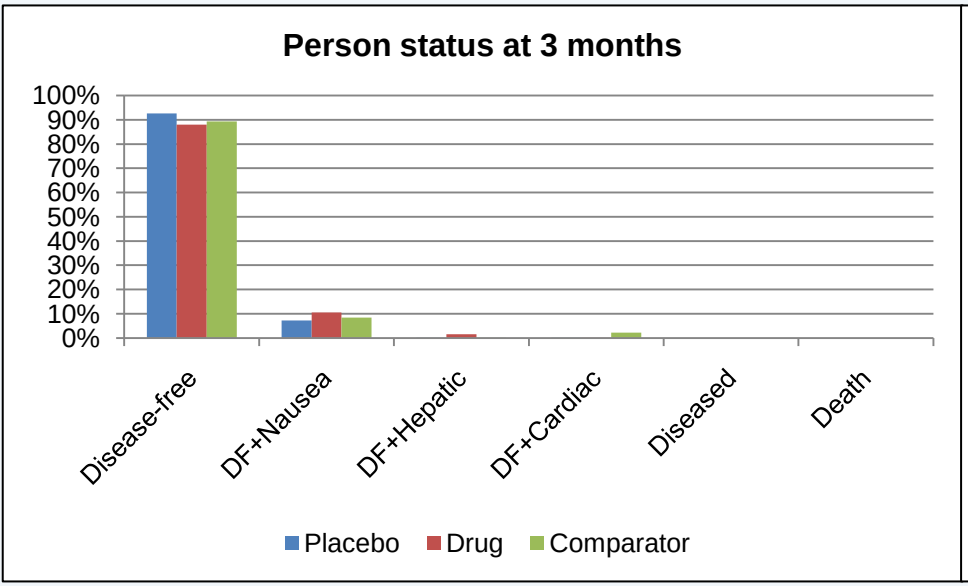
A few examples include:

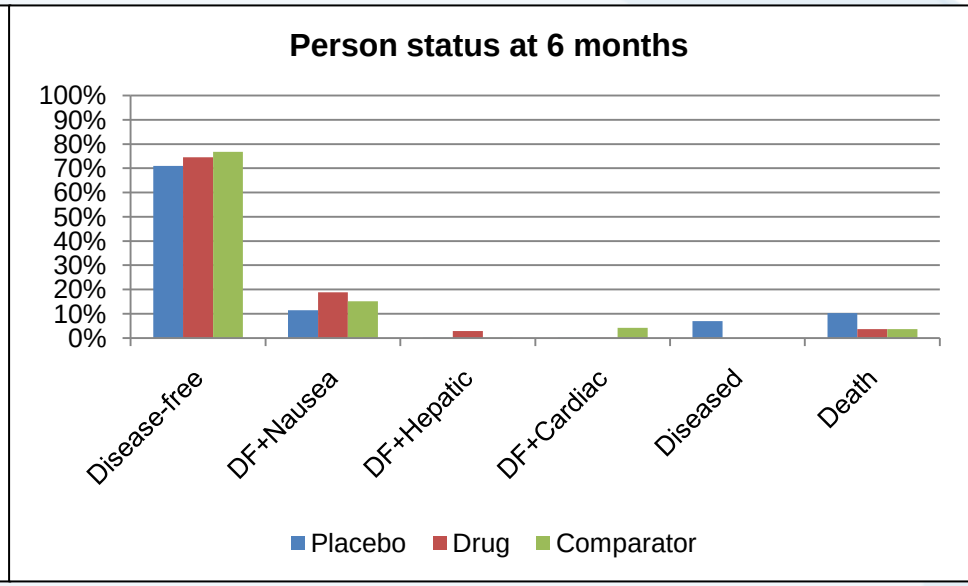
- **Decision Trees**
- **Markov Models**
- **Discrete-event simulation**
- **etc.**

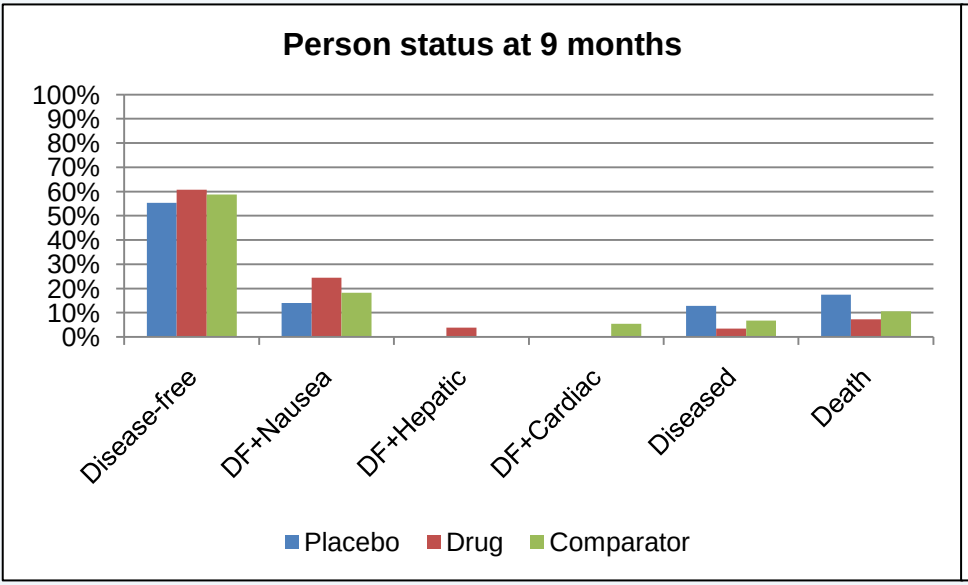
Your choice may depend on decisions around :

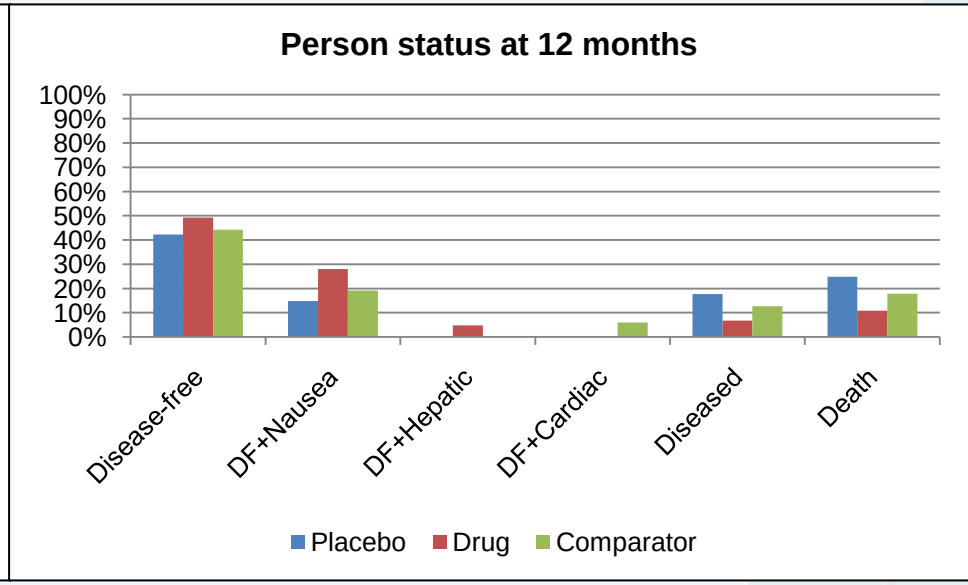
- **Data** (individual patient data vs. summary statistics)
- **Uncertainty** (patient, outcome & parameter variability)
- **Output Metrics** (Person-time, INB, QALYs, etc.)

Visualization of Output:
No. of patients in each health state by month

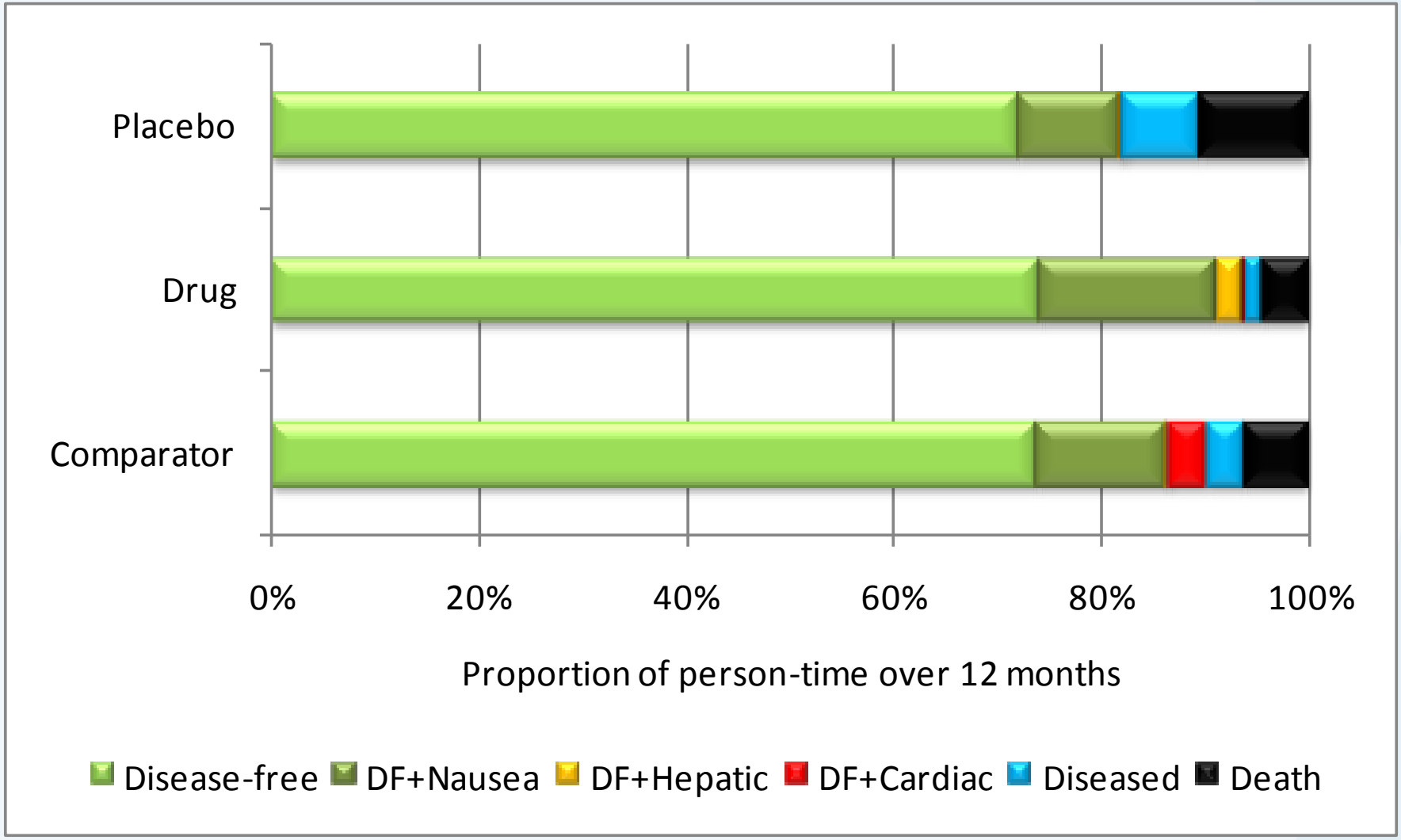








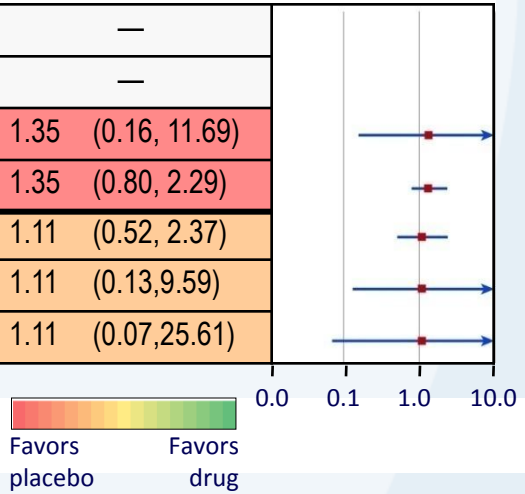
Visualization of Output:
Person-time in each health state by month 12



BRAT Framework Key Benefit-Risk Summary Table

- Top level representation of information in the framework
- The most critical view that decision makers will have on the data

		Outcome	Incidence: study drug (%)	Incidence: placebo (%)	Adjusted RR (95% CI)	Forest Plot of Adjusted RR (Log Scale)
Benefits	Cardio-vascular Issues	Angina requiring CABG	0.11	0.19	0.59 (0.32, 1.10)	
		Coronary heart disease death	1.52	1.65	1.00 (0.64, 1.56)	
		Lipid levels meet target*	67.00	29.00	2.12 (1.77, 2.55)	
		Nonfatal myocardial infarction	0.66	1.30	0.51 (0.05, 5.56)	
	Ischemic Stroke	Fatal ischemic stroke	0.91	1.73	0.57 (0.35, 0.95)	
		Nonfatal ischemic stroke	2.34	2.88	0.84 (0.71, 0.98)	
Risks	Liver Damage	Hepatitis with hospitalization	—	—	—	
		Hepatitis without hospitalization	—	—	—	
		Liver failure*	0.013	0.0095	1.35 (0.16, 11.69)	
		Persistently elevated transaminases	0.26	0.19	1.35 (0.80, 2.29)	
	Muscle Damage	Myopathy	0.11	0.10	1.11 (0.52, 2.37)	
		Rhabdomyolysis*	0.011	0.01	1.11 (0.13,9.59)	
		Severe rhabdomyolysis leading to kidney failure*	0.0006	0.0005	1.11 (0.07,25.61)	



* Mock data for visualization purpose only

Levitan and Andrews, "Example Application of PhRMA BRAT (Benefit-Risk Action Team) Framework", Assessing Benefits and Risks of Medicinal Products in Regulatory Decisions, DIA, Nov, 2009

Evaluate results

Check the robustness of the results

- Are the assumptions still reasonable?
- Do sensitivity analyses show which factors drive the results?
- Do utilities or preference weights shift the emphasis?

Does the analysis need more data or fewer assumptions?

Is the information provided sufficient for clear & transparent decision-making?

Concluding thoughts

- The goal is to gain a "*shared understanding*" of benefit:risk trade-offs between alternative treatments
- Explicitly stated data & modeling assumptions add transparency to direct and indirect comparisons
- The primary limitation is often available data rather than methodology
- Stakeholders can explore a range of benefit:risk trade-offs, from a patient to societal perspectives
- Statisticians have a significant opportunity to lead this quantitative process to meaningfully inform the appropriate use of medical products

Benefit-risk analysis: enabling the view of the bigger picture

Questions?

Mike Colopy
mike.w.colopy@gsk.com

Patrick Ryan
patrick.b.ryan@gsk.com

The End

Backup Slides

Definitions

Term	Definition
Discrete-event simulation	Models events that occur at an instant in time, marking a change of state; assess individual patients sampled from distributions of baseline characteristics.
Markov model	Models uncertain events as transitions between health states; assesses a cohort's risk over time. Transition probability does not depend on previous transition.
Uncertainty	Variability in patients, subgroups, outcomes, parameters and model specifications.
Utility	Weighted conversion used to normalize benefits and harms to the same scale; e.g. health-related quality of life or conjoint preference weights.
Value Tree	

Recommended Reading

Lynd L and O-Brien B, Advances in risk-benefit evaluation using probabilistic simulation methods: an application to the prophylaxis of deep vein thrombosis, Journal of Clinical Epidemiology 57 (2004) 795–803. Keywords: **Monte Carlo simulation**.

Lynd L, et.al. Using the Incremental Net Benefit Framework for Quantitative Benefit–Risk Analysis in Regulatory Decision-Making—A Case Study of Alosetron in Irritable Bowel Syndrome, Value in Health, 2009. Keywords: **Discrete-event simulation**.

Mussen F, et. al. A quantitative approach to benefit-risk assessment of medicines – part 1: The development of a new model using multi-criteria decision analysis, Pharmacoepidemiology and Drug Safety, 2007. **Keyword: Value tree**.

Minelli C, et. al., Benefits and harms associated with hormone replacement therapy: clinical decision analysis, BMJ 2004. Keywords: **Markov Chain Monte Carlo Simulation.**