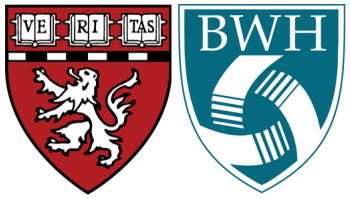
Addressing Uncertainties in the Evaluation of Pharmaceutical Benefits and Harms

during the market access phase

Sebastian Schneeweiss, MD, ScD

Professor of Medicine and Epidemiology



Division of Pharmacoepidemiology and Pharmacoeconomics,

Dept of Medicine, Brigham & Women's Hospital/ Harvard Medical School

Potential conflicts of interest

- Co-Chair, Methods Core of the Mini Sentinel System (FDA)
- Member, PCORI Methods Committee
- Consulting in past year:
  - WHISCON LLC, Aetion Inc. (incl. shares)
- Investigator-initiated research grants to the Brigham from Novartis, Boehringer-Ingelheim
- Multiple grants from NIH, PCORI

Sources of Uncertainty

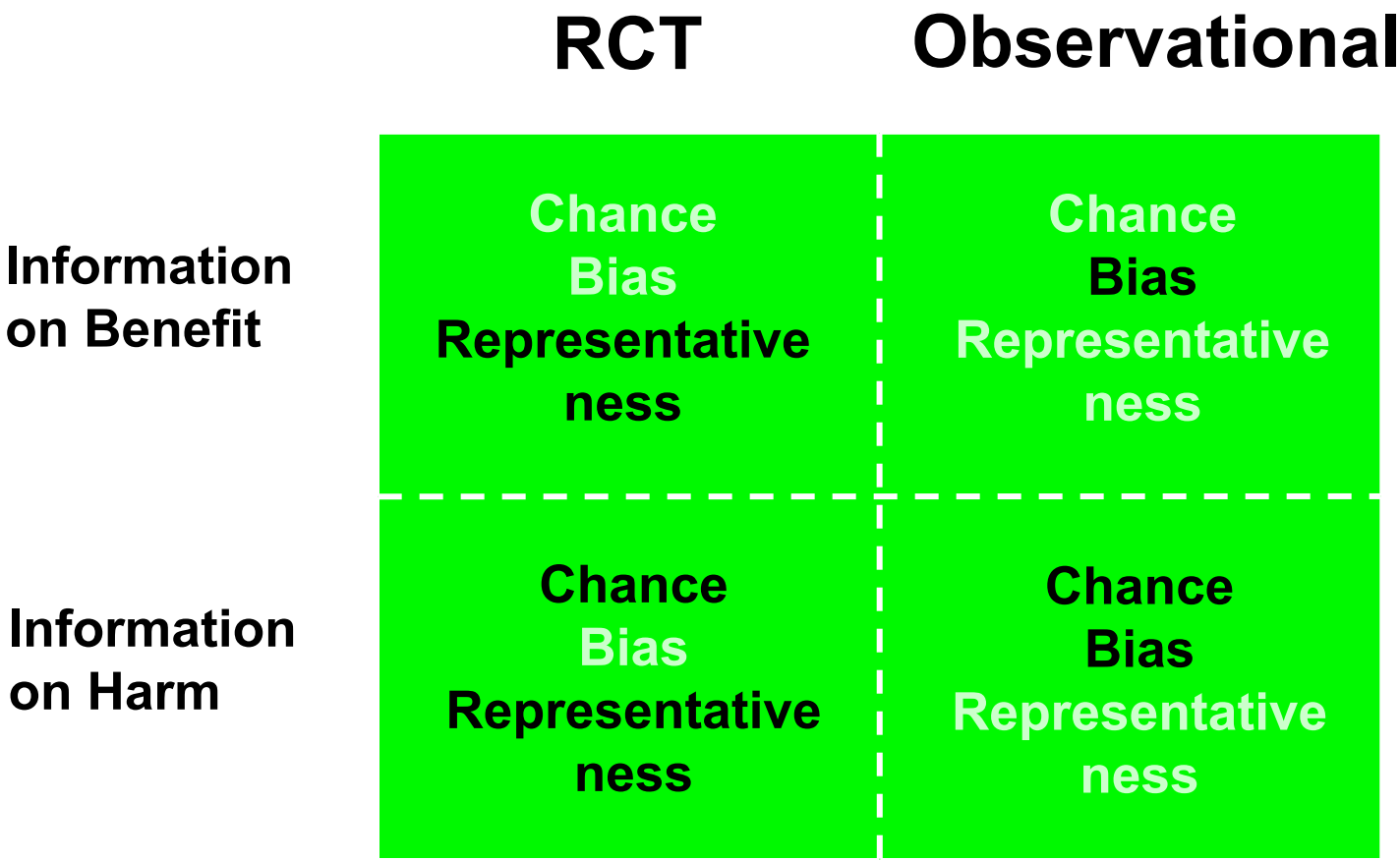
What uncertainties do we need to expect in the evidence that is used for Benefit-Harm assessment?

Sources for uncertainty	
Chance	Internal validity
Bias • Confounding/informative censoring • Time-related biases • Surveillance bias • Misclassification • …	
Representativeness • Population • Severity • Comparator	External validity

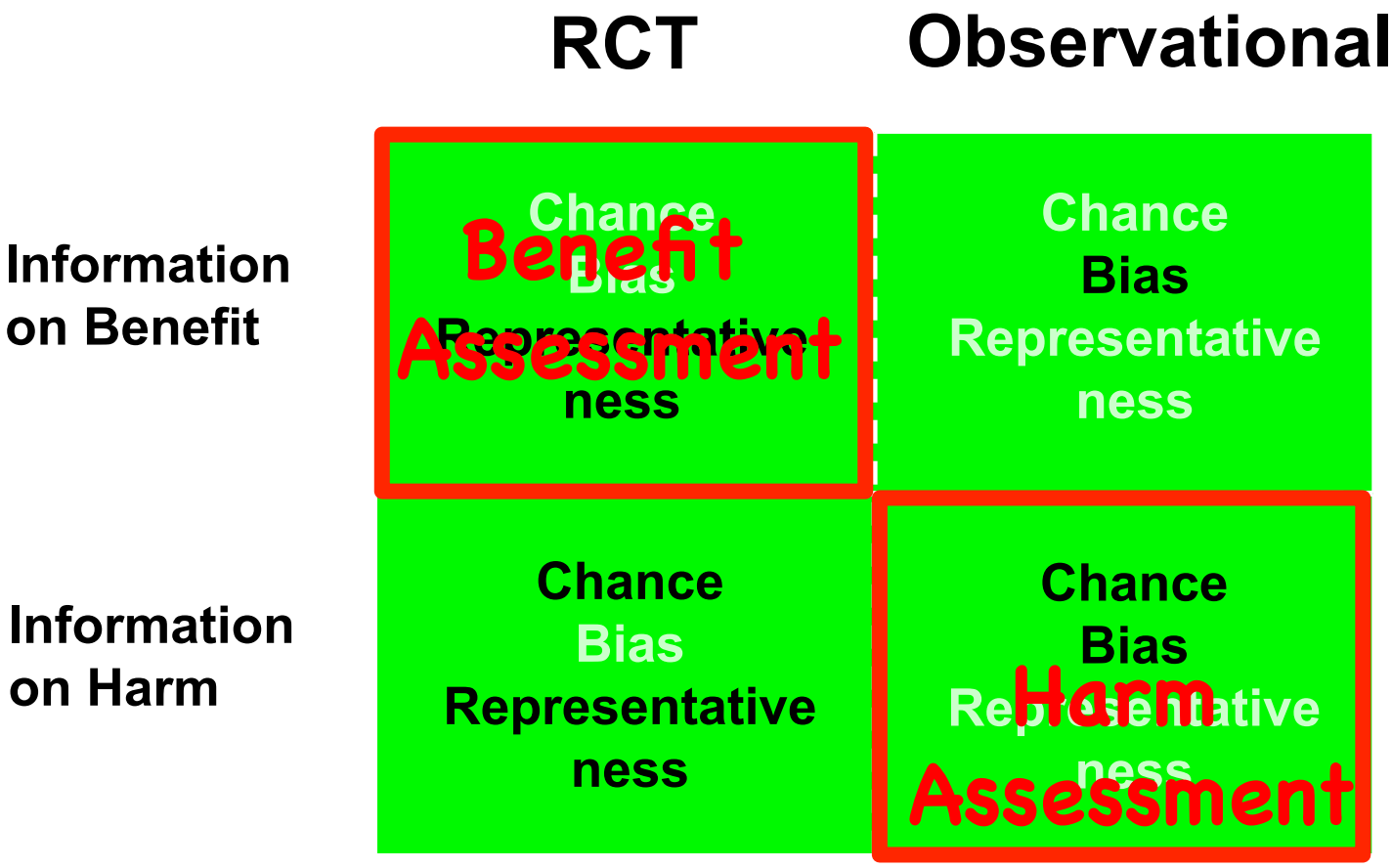
Quantifying Uncertainty

Sources for uncertainty	Quantification of uncertainty
Chance	95% confidence intervals
Bias • Confounding/informative censoring • Time-related biases • Surveillance bias • Misclassification	• Negative control outcomes • Emulating trial populations • Bias modeling • Sensitivity analyses • Plasmode simulation studies
Representativeness • Population • Severity • Adherence • Comparator	Subgroups

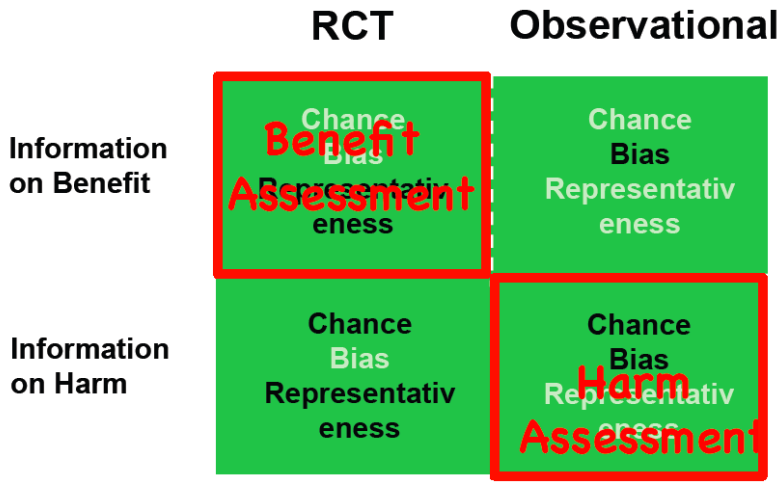
Sources of Uncertainty by Study Design (an embarrassing generalization)



Typical Information Sources for Benefit-Harm Assessment



Typical Information Sources for Benefit-Harm Assessment

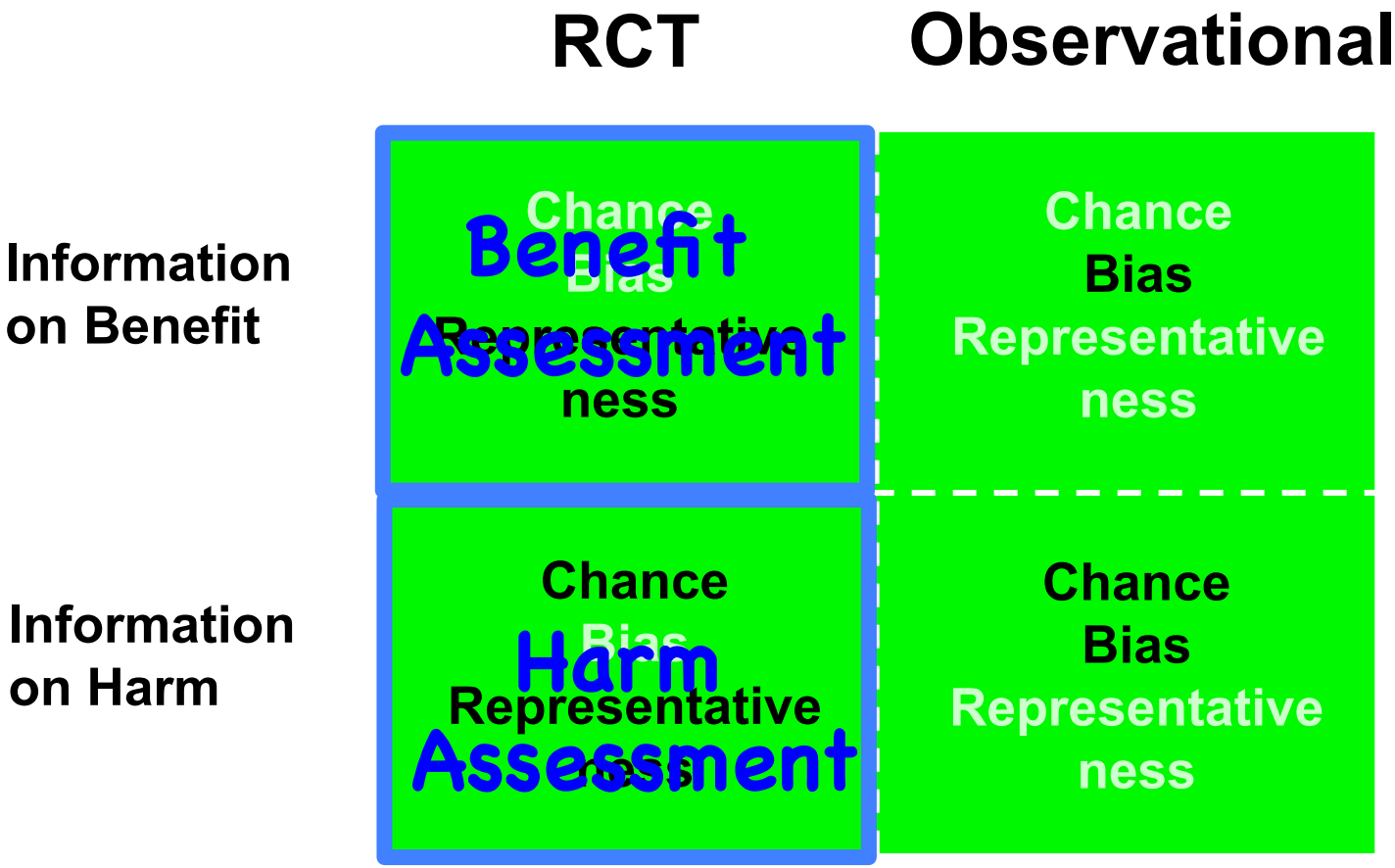


Do we really want to

- Mix valid but highly selective efficacy information from RCTs
- with generalizable but less valid safety information?

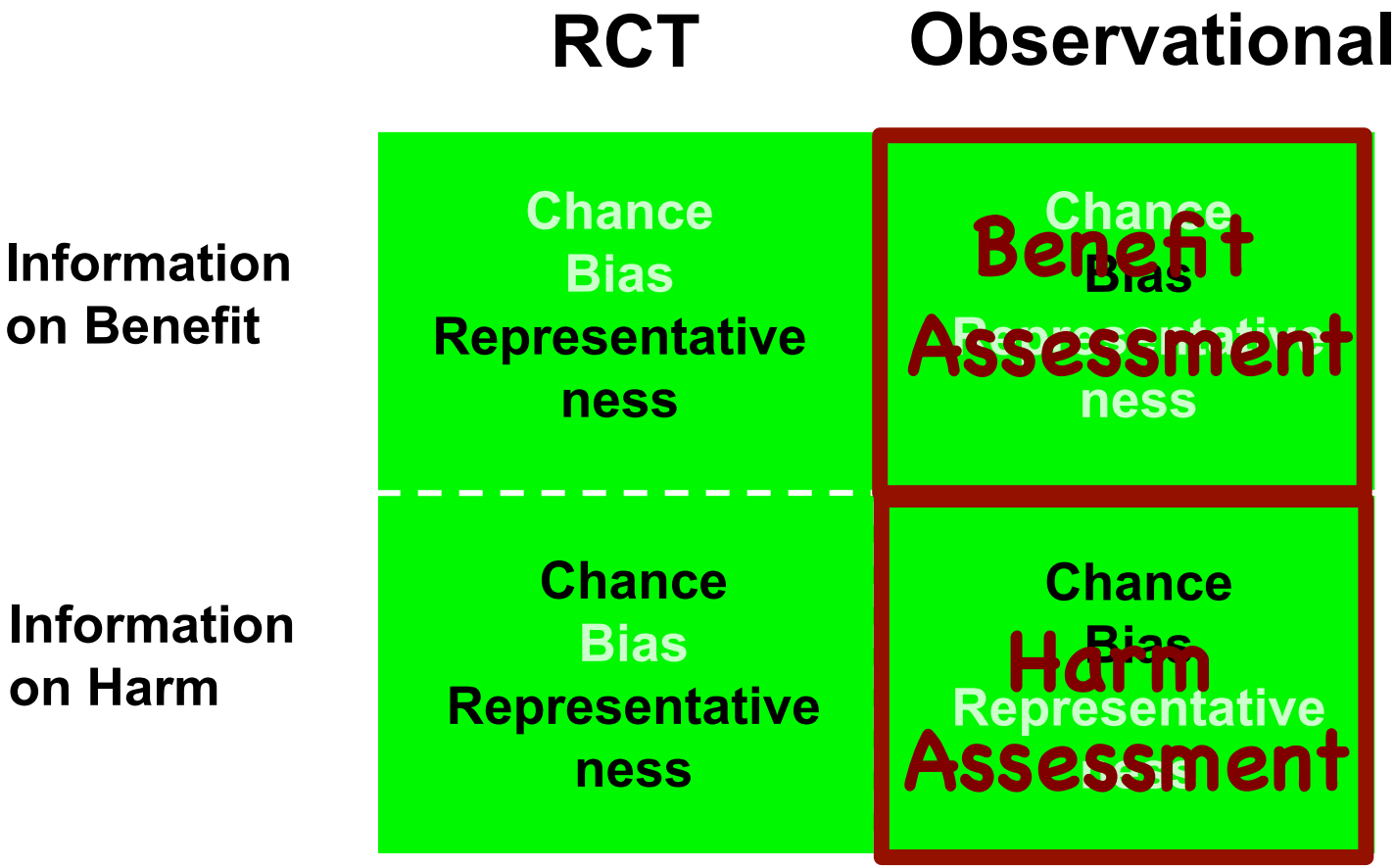
Stay in RCT-land?

Comparable + valid but less representative?



Operate in observation-land?

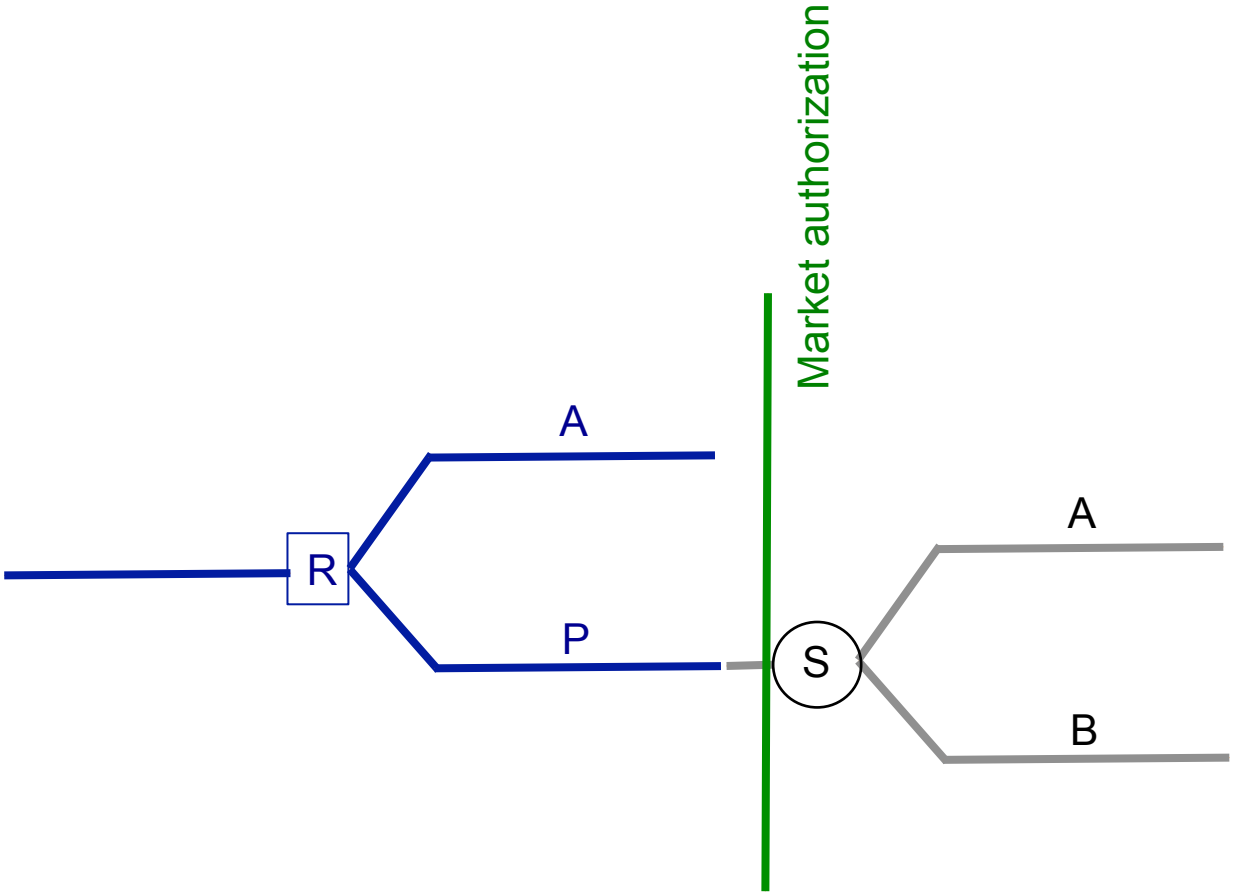
Representative and high power but less valid?



A coordinate study portfolio

- Often we need multiple studies with different data sources (prim/sec) and different designs
- Optimal way to arrange multiple studies:
  - To reduce chance
  - To characterize representativeness
  - To characterize (and reduce) bias
  - To complement each other in speed, validity, precision, generalizability
  - To collectively provide most valid and comprehensive information for decision makers with least resources?

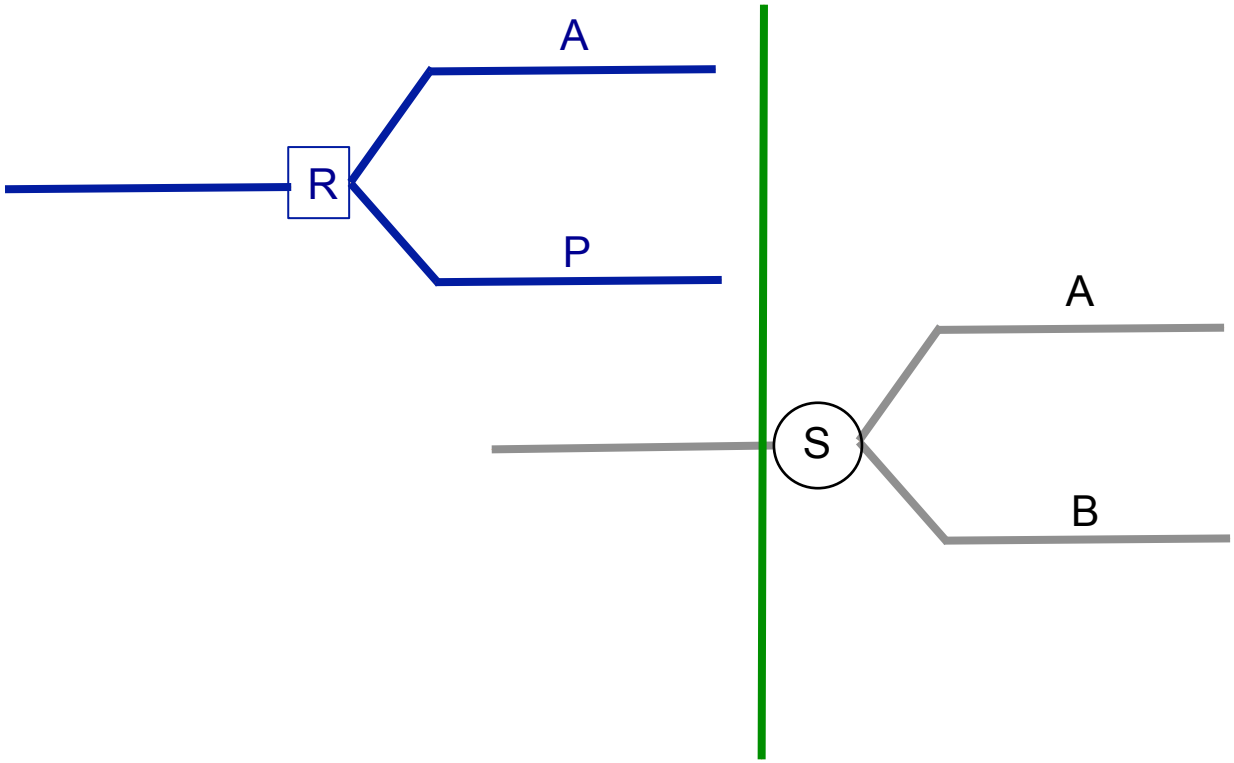
1)RCT follow-on study



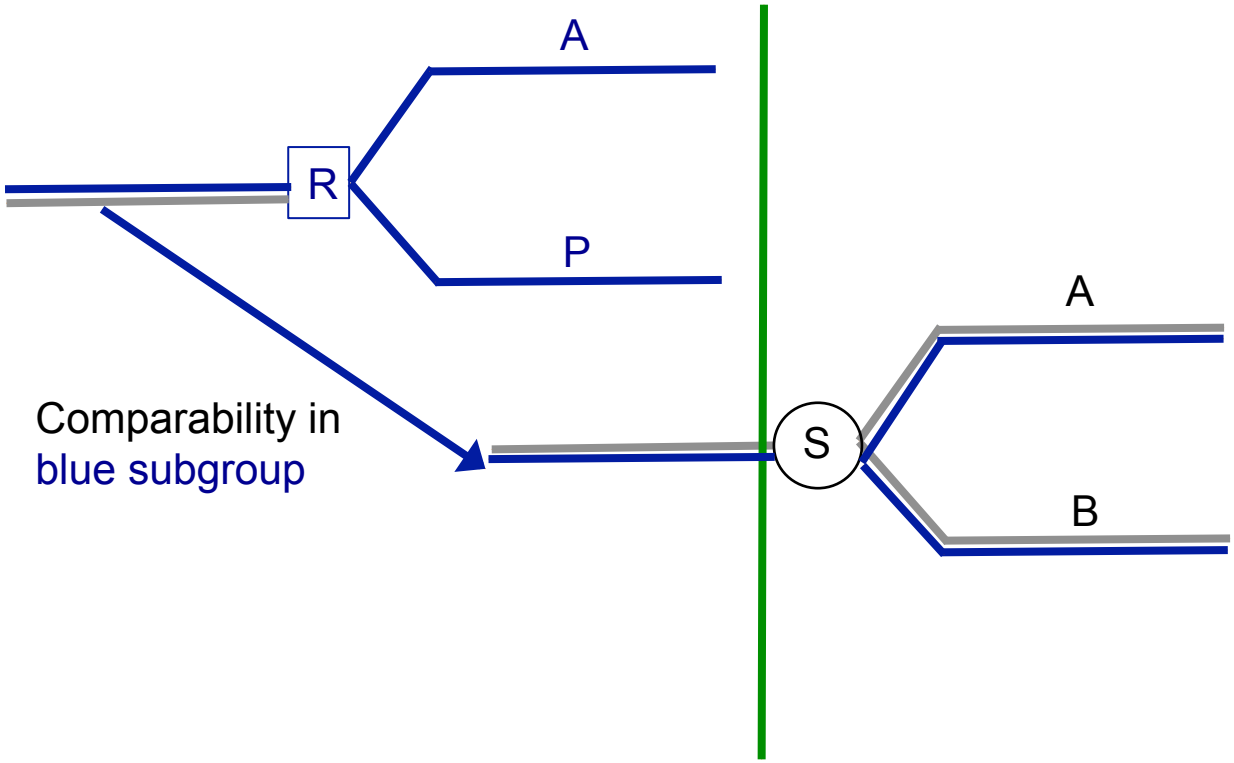
Observational follow-on study:

Assess non-randomized finding in RCT population

2) Observational database study (claims)



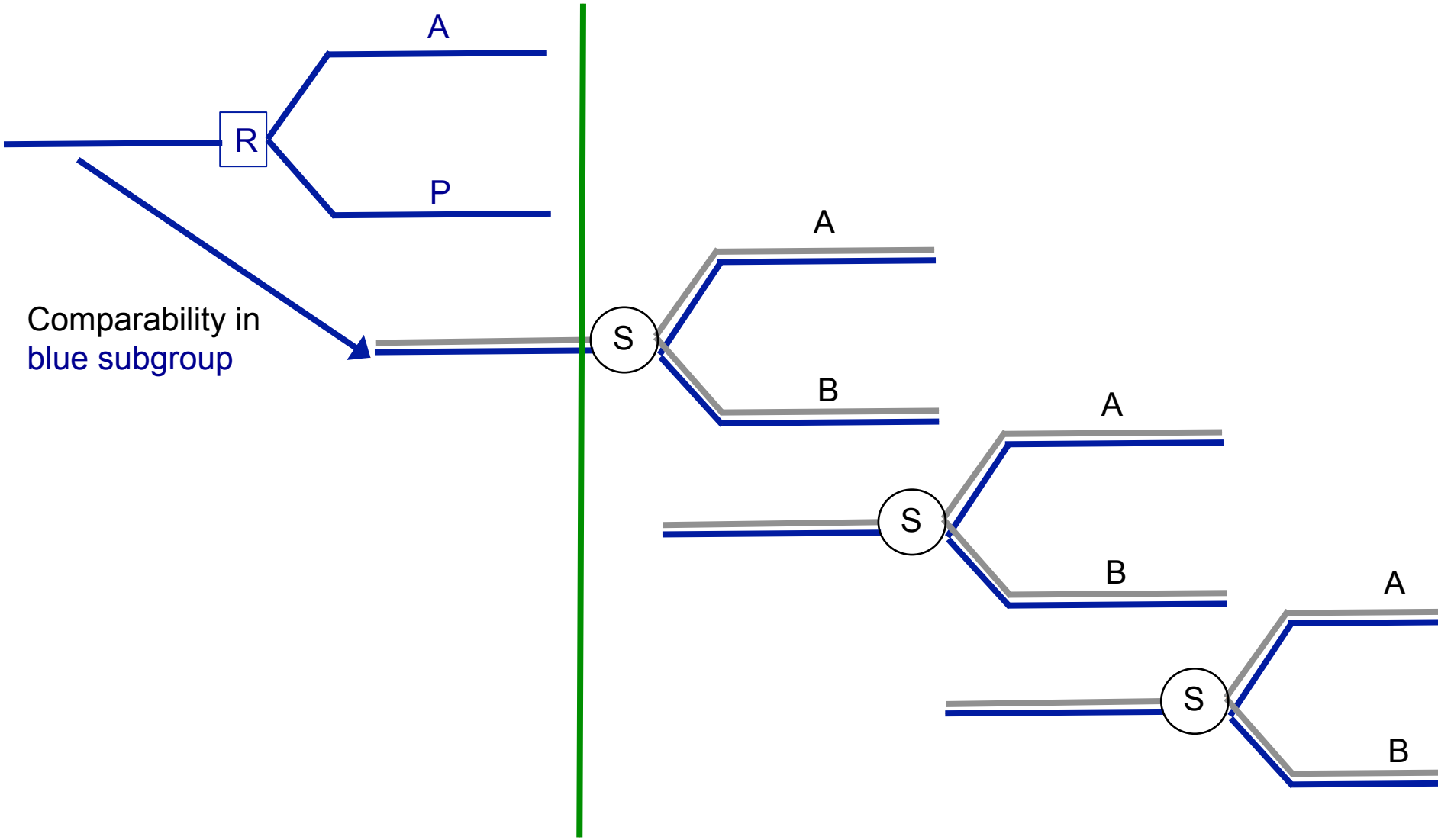
2) Observational database study (claims)



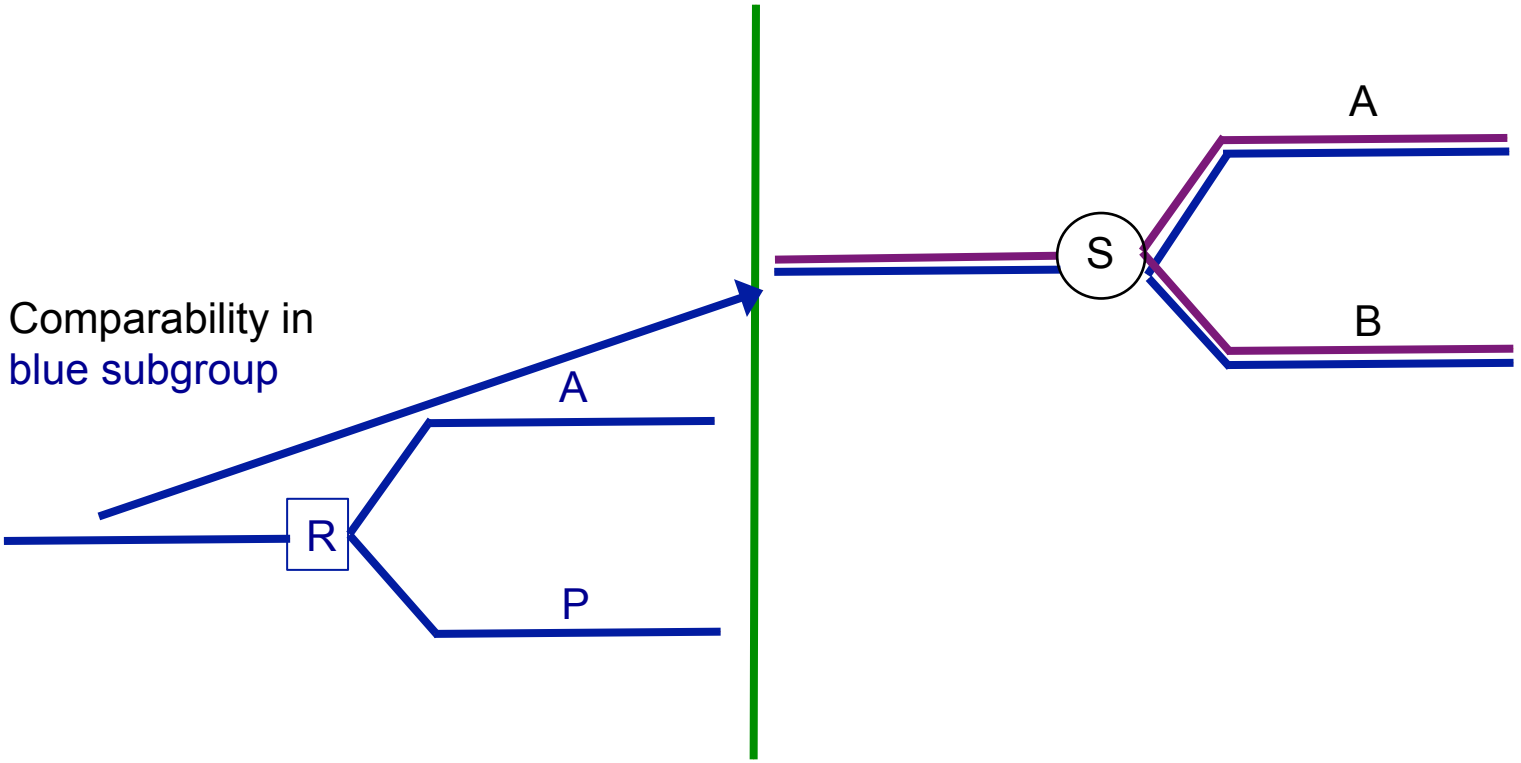
Identify RCT-like subgroup in database study:

Reproducing RCT findings to calibrate observational findings

2b) Sequential database study (M-S)



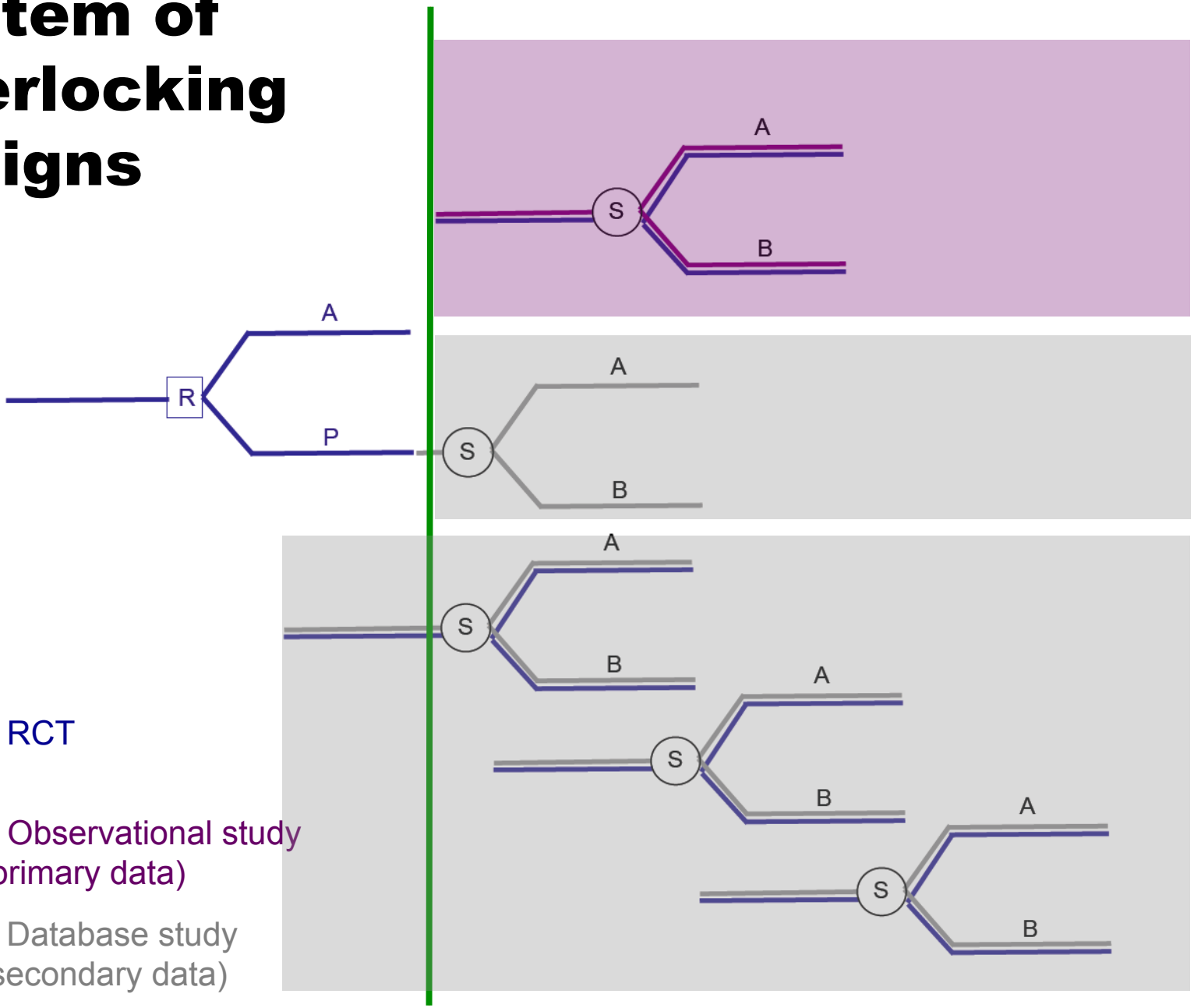
3) Observational study (primary data)



Identify RCT-like subgroup in cohort study w/ primary data:

Reproducing RCT findings to calibrate observational findings

System of interlocking designs



Active Surveillance &false decision making

False positive alerts:

Societal cost:

- Withholding a safe and effective drug from some selected patient groups or from all.

Causes:

- Lack of confounder control
- Multiple testing

Alert generation process:

- Process ctrl rules
- Sequential testing (SPRT)
- Gamma shrinkage
- Estimation projection
- Disproportionality measures

False negative alerts:

Societal cost:

- Exposing patients to an unnecessary risk
- Marketing with inappropriate risk information

Causes:

- Lack of confounder control
- Insufficient precision

Correct ("true") alerts:

Societal gain:

- Makes new risk information available quickly
- Removes or restricts unsafe medications quickly

Avorn, Schneeweiss NEJM 2010

Threshold is defined by benefit-harm trade-offs

BENEFIT

- Availability of an alternative drug
- Compar. effectiveness of drug vs. alternative drug
- Value of benefits (life-saving vs. mild skin rash)
- Prognosis of user population (cancer pats vs. babies)

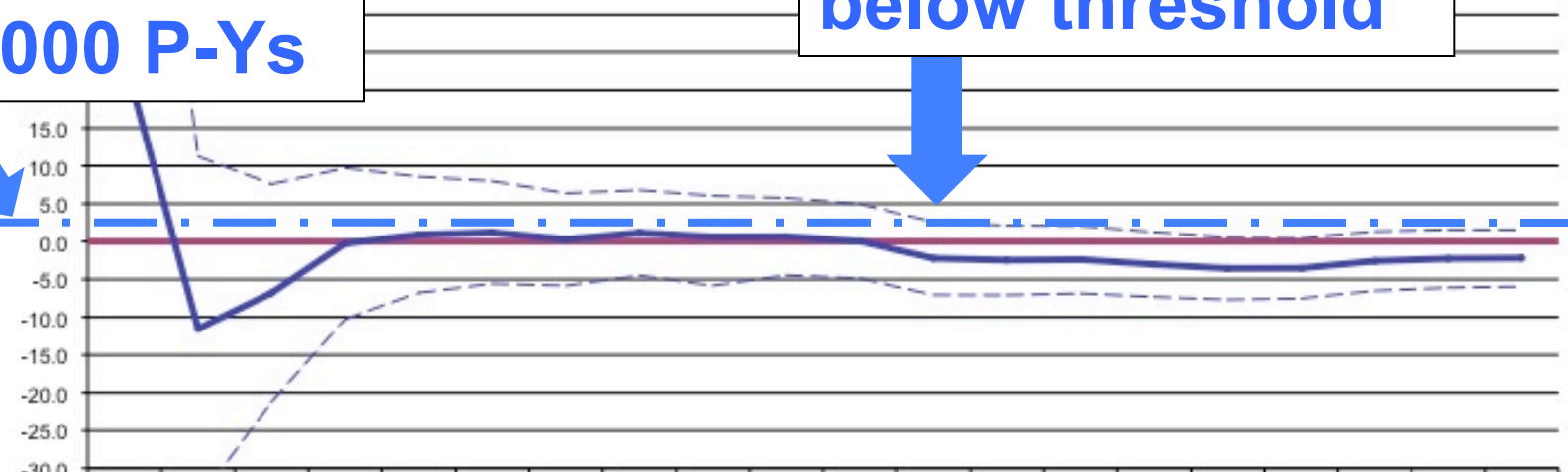
HARM

- Frequency of adverse effect (B-H analysis is based on absolute risks)
- Seriousness of adverse event (death vs. nose bleed)

Rosuvastatin and DM

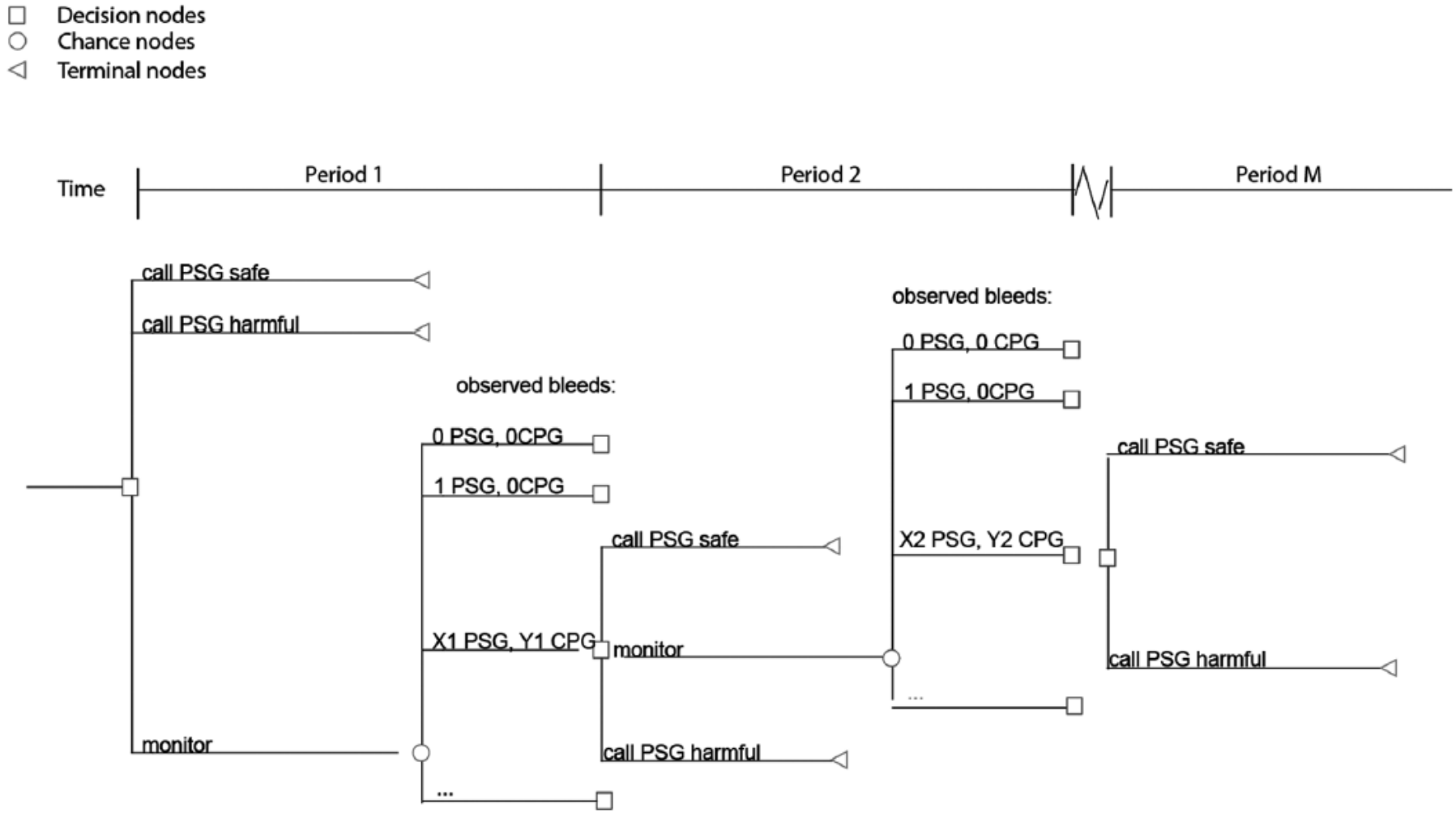
Safety threshold at 2.5/1,000 P-Ys

Upper 95% CI below threshold



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Lower 95% confidence interval	-38.29	-34.33	-21.18	-10.24	-6.77	-5.57	-5.85	-4.51	-5.84	-4.46	-4.88	-7.06	-7.09	-6.86	-7.32	-7.69	-7.52	-6.51	-6.10	-5.96
Cumulative rate difference	24.22	-11.54	-6.79	-0.26	0.90	1.21	0.27	1.15	0.62	0.65	0.04	-2.24	-2.48	-2.40	-3.04	-3.57	-3.54	-2.59	-2.27	-2.21
Upper 95% confidence interval	86.74	11.25	7.60	9.71	8.58	7.99	6.39	6.81	6.04	5.76	4.96	2.59	2.13	2.06	1.24	0.56	0.45	1.33	1.56	1.55
Cumulative events: rosuvastatin	13	30	56	127	199	267	321	370	403	424	446	501	560	630	681	731	782	821	841	859
Cumulative events: atorvastatin	11	40	70	135	208	283	354	406	454	481	517	614	688	774	849	922	985	1013	1032	1055
Cumulative person-years: rosuvastatin	144	700	1482	3094	4983	6489	7905	9090	10039	10745	11482	12563	13941	15251	16581	17867	19161	19839	20480	21098
Cumulative person-years: atorvastatin	167	735	1570	3268	5329	7086	8776	10265	11488	12393	13322	14578	16131	17710	19248	20729	22210	23036	23814	24580

Sequential Value of Information approach



Patrick et al. MDM 2013

Inputs for a VOI decision analysis

Input	Base Case Value
Person-time exposed to prasugrel during each monitoring period	13 person-years
Priors for additional safety and efficacy outcomes (rate per 100 person-years), clopidogrel	Nonfatal MI: 5.93 Nonfatal stroke: 1.14 Death: 1.27
Relative rates of safety outcomes, prasugrel v. clopidogrel	Nonfatal MI: 0.76 Nonfatal stroke: 1.02 Death: 0.95
Health loss weights (expressed as fractions of life expectancy)	
GI bleed	0.001
Nonfatal MI	0.09
Nonfatal stroke	0.25
Death	1

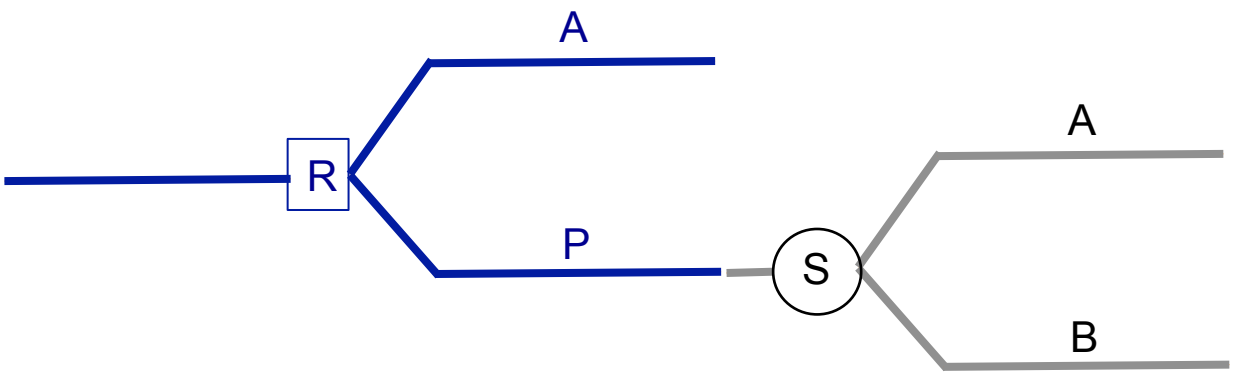
GI, gastrointestinal; MI, myocardial infarction.

Patrick et al. MDM 2013

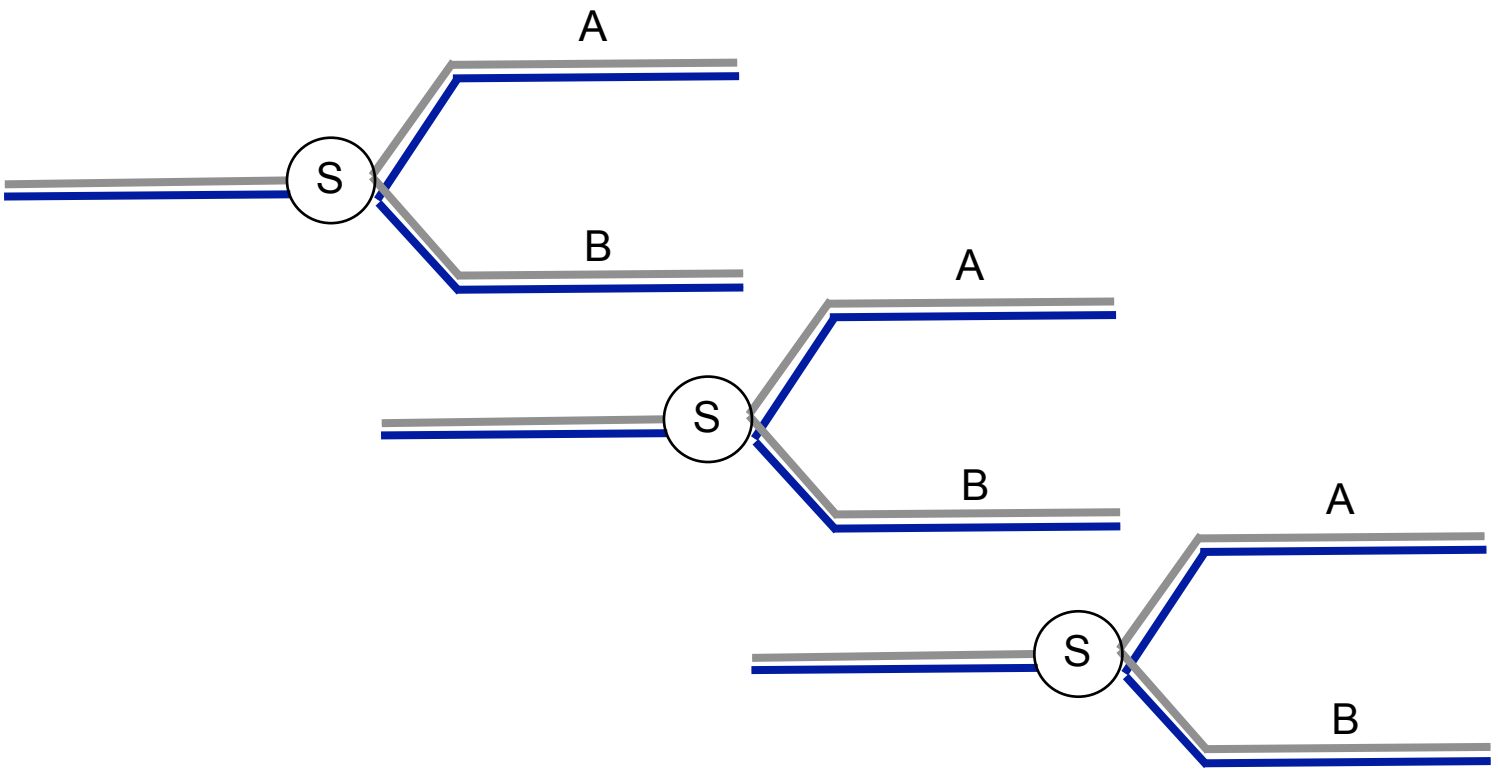
Conclusion

- Distinct sources of uncertainty: chance, bias, representativeness
- Set of tools to assess uncertainty; difficult for bias
- A system of interlocking studies will help to more effectively quantify uncertainty
- The needs for formal B-H approaches is most obvious in monitoring settings

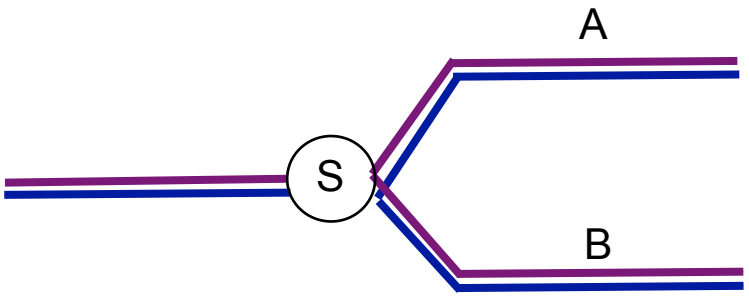
RCT follow-on study



Sequential database study (M-S)



Registry study with PROs



Identify RCT-like subgroup in observational study: Reproducing RCT findings

A litany of approaches that will help reduce uncertainty in observational studies

- Active comparators
- New users
- PS matching or trimming
- hd-PS analyses
- Marginal structural models
- Additional data
- Validation studies
- Sensitivity analyses
- Negative control outcomes
- Etc. etc.

Monitoring for rhabdomyolysis:
cerivastatin (Baycol) vs. atorvastatin (Lipitor)

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Lower 95% confidence interval	-99.00	-99.00												
Cumulative rate difference	0.00	0.00												
Upper 95% confidence interval	99.00	99.00												
Cumulative events: cerivastatin	0	0												
Cumulative events: atorvastatin	0	0												
Cumulative person-years cerivastatin	19	60												
Cumulative person-years: atorvastatin	26	65												

Source population: only 250,000 Medicare beneficiaries
(compare to 100,000,000 from Mini-Sentinel)

Gagne JJ et al. 2011

Monitoring for rhabdomyolysis:
cerivastatin (Baycol) vs. atorvastatin (Lipitor)

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Lower 95% confidence interval	-99.00	-99.00	-99.00											
Cumulative rate difference	0.00	0.00	0.00											
Upper 95% confidence interval	99.00	99.00	99.00											
Cumulative events: cerivastatin	0	0	0											
Cumulative events: atorvastatin	0	0	0											
Cumulative person-years cerivastatin	19	60	124											
Cumulative person-years: atorvastatin	26	65	127											

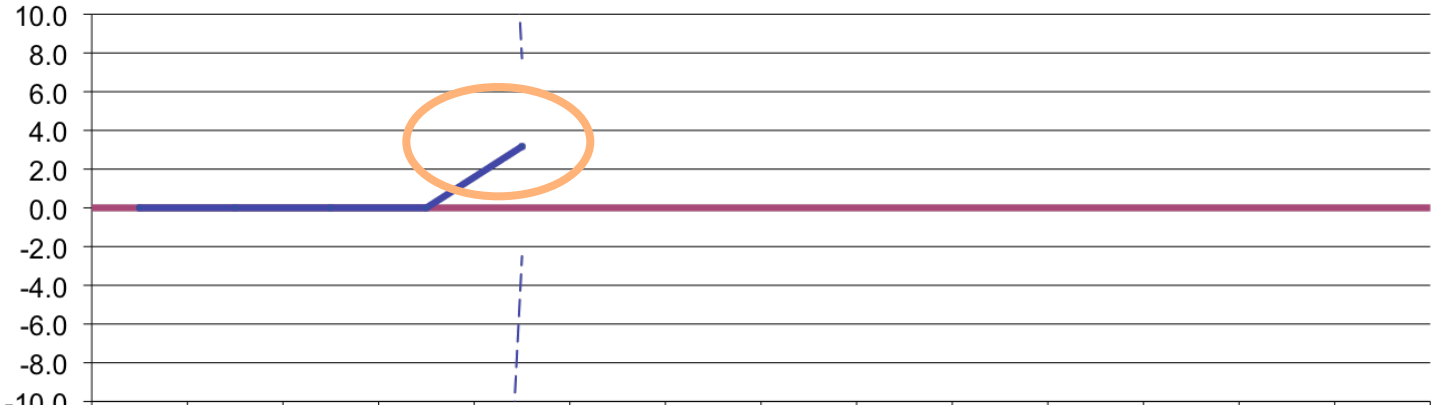
Gagne JJ et al. 2011

Monitoring for rhabdomyolysis:
cerivastatin (Baycol) vs. atorvastatin (Lipitor)

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Lower 95% confidence interval	-99.00	-99.00	-99.00	-99.00										
Cumulative rate difference	0.00	0.00	0.00	0.00										
Upper 95% confidence interval	99.00	99.00	99.00	99.00										
Cumulative events: cerivastatin	0	0	0	0										
Cumulative events: atorvastatin	0	0	0	0										
Cumulative person-years cerivastatin	19	60	124	197										
Cumulative person-years: atorvastatin	26	65	127	218										

Gagne JJ et al. 2011

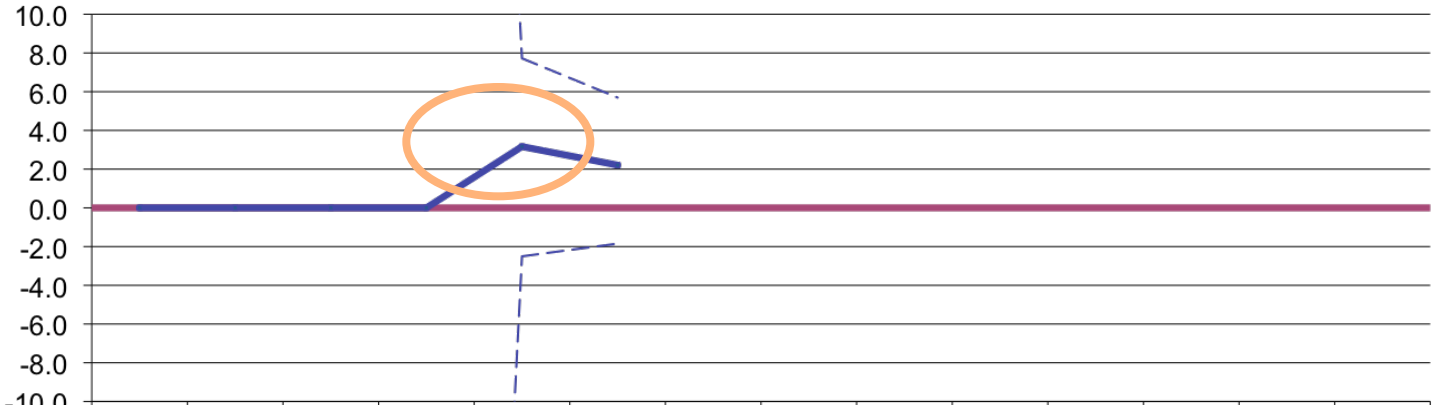
Monitoring for rhabdomyolysis:
cerivastatin (Baycol) vs. atorvastatin (Lipitor)



	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Lower 95% confidence interval	-99.00	-99.00	-99.00	-99.00	-2.50									
Cumulative rate difference	0.00	0.00	0.00	0.00	3.17									
Upper 95% confidence interval	99.00	99.00	99.00	99.00	7.72									
Cumulative events: cerivastatin	0	0	0	0	1									
Cumulative events: atorvastatin	0	0	0	0	0									
Cumulative person-years cerivastatin	19	60	124	197	316									
Cumulative person-years: atorvastatin	26	65	127	218	348									

Gagne JJ et al. 2011

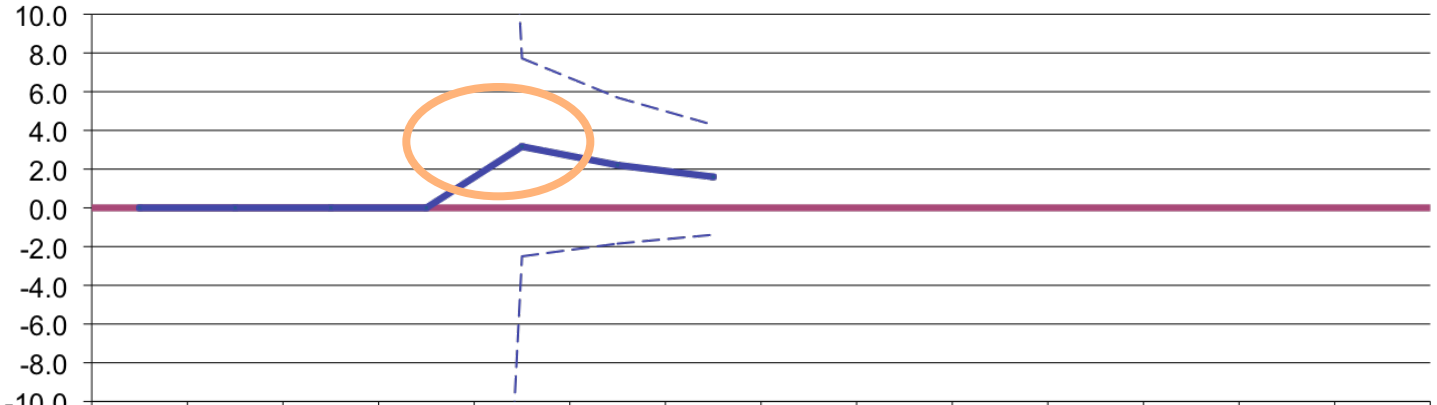
Monitoring for rhabdomyolysis:
cerivastatin (Baycol) vs. atorvastatin (Lipitor)



	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Lower 95% confidence interval	-99.00	-99.00	-99.00	-99.00	-2.50	-1.85								
Cumulative rate difference	0.00	0.00	0.00	0.00	3.17	2.21								
Upper 95% confidence interval	99.00	99.00	99.00	99.00	7.72	5.70								
Cumulative events: cerivastatin	0	0	0	0	1	1								
Cumulative events: atorvastatin	0	0	0	0	0	0								
Cumulative person-years cerivastatin	19	60	124	197	316	453								
Cumulative person-years: atorvastatin	26	65	127	218	348	497								

Gagne JJ et al. 2011

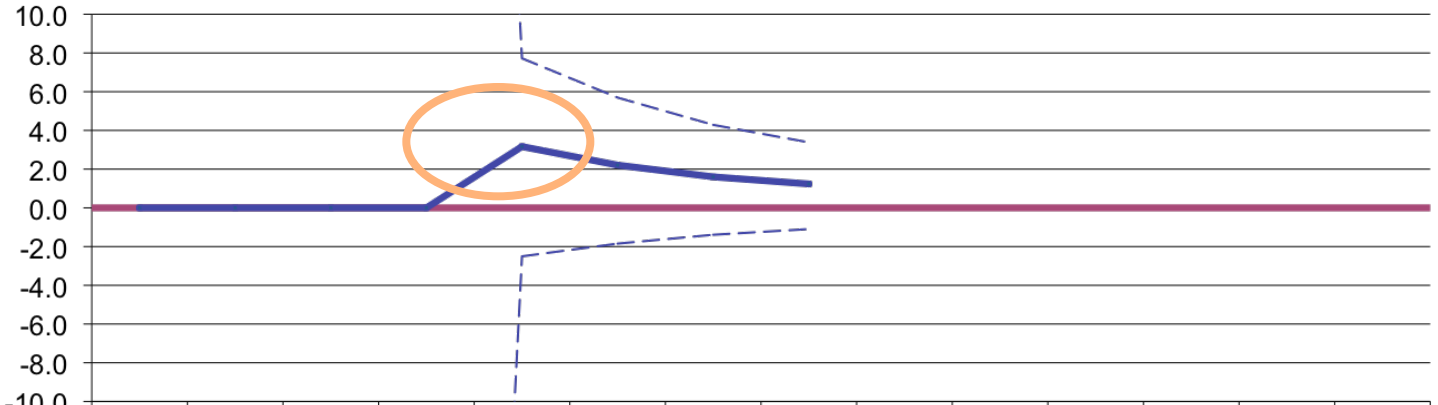
Monitoring for rhabdomyolysis:
cerivastatin (Baycol) vs. atorvastatin (Lipitor)



	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Lower 95% confidence interval	-99.00	-99.00	-99.00	-99.00	-2.50	-1.85	-1.39							
Cumulative rate difference	0.00	0.00	0.00	0.00	3.17	2.21	1.60							
Upper 95% confidence interval	99.00	99.00	99.00	99.00	7.72	5.70	4.29							
Cumulative events: cerivastatin	0	0	0	0	1	1	1							
Cumulative events: atorvastatin	0	0	0	0	0	0	0							
Cumulative person-years cerivastatin	19	60	124	197	316	453	625							
Cumulative person-years: atorvastatin	26	65	127	218	348	497	681							

Gagne JJ et al. 2011

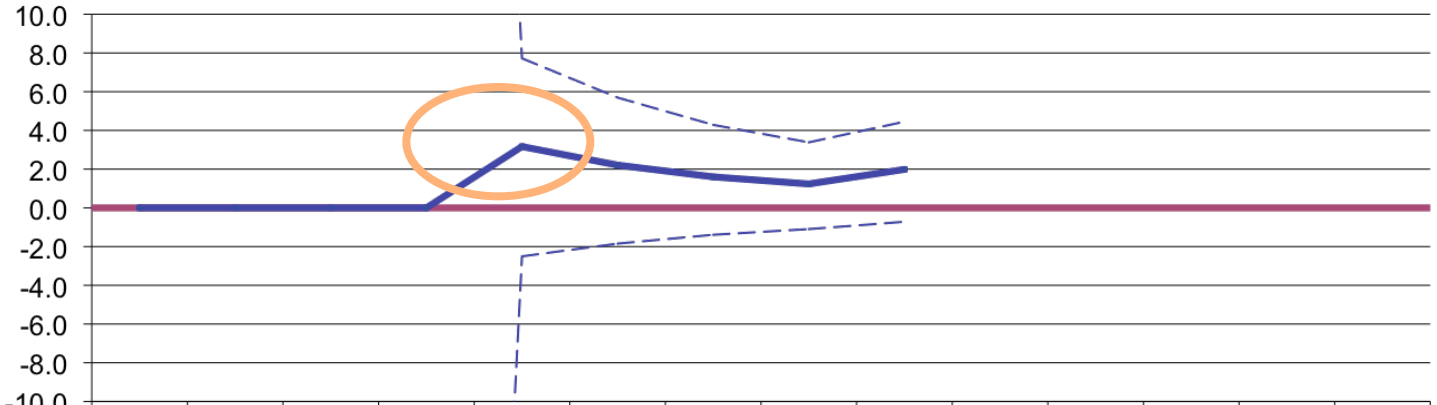
Monitoring for rhabdomyolysis:
cerivastatin (Baycol) vs. atorvastatin (Lipitor)



	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Lower 95% confidence interval	-99.00	-99.00	-99.00	-99.00	-2.50	-1.85	-1.39	-1.10						
Cumulative rate difference	0.00	0.00	0.00	0.00	3.17	2.21	1.60	1.24						
Upper 95% confidence interval	99.00	99.00	99.00	99.00	7.72	5.70	4.29	3.38						
Cumulative events: cerivastatin	0	0	0	0	1	1	1	1						
Cumulative events: atorvastatin	0	0	0	0	0	0	0	0						
Cumulative person-years cerivastatin	19	60	124	197	316	453	625	809						
Cumulative person-years: atorvastatin	26	65	127	218	348	497	681	877						

Gagne JJ et al. 2011

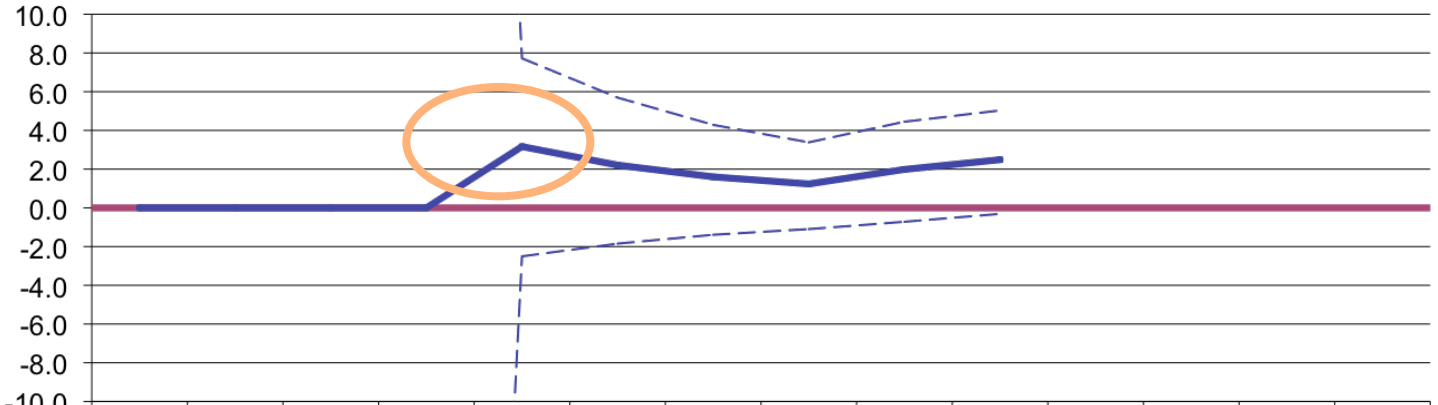
Monitoring for rhabdomyolysis:
cerivastatin (Baycol) vs. atorvastatin (Lipitor)



	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Lower 95% confidence interval	-99.00	-99.00	-99.00	-99.00	-2.50	-1.85	-1.39	-1.10	-0.72					
Cumulative rate difference	0.00	0.00	0.00	0.00	3.17	2.21	1.60	1.24	1.99					
Upper 95% confidence interval	99.00	99.00	99.00	99.00	7.72	5.70	4.29	3.38	4.45					
Cumulative events: cerivastatin	0	0	0	0	1	1	1	1	2					
Cumulative events: atorvastatin	0	0	0	0	0	0	0	0	0					
Cumulative person-years cerivastatin	19	60	124	197	316	453	625	809	1007					
Cumulative person-years: atorvastatin	26	65	127	218	348	497	681	877	1084					

Gagne JJ et al. 2011

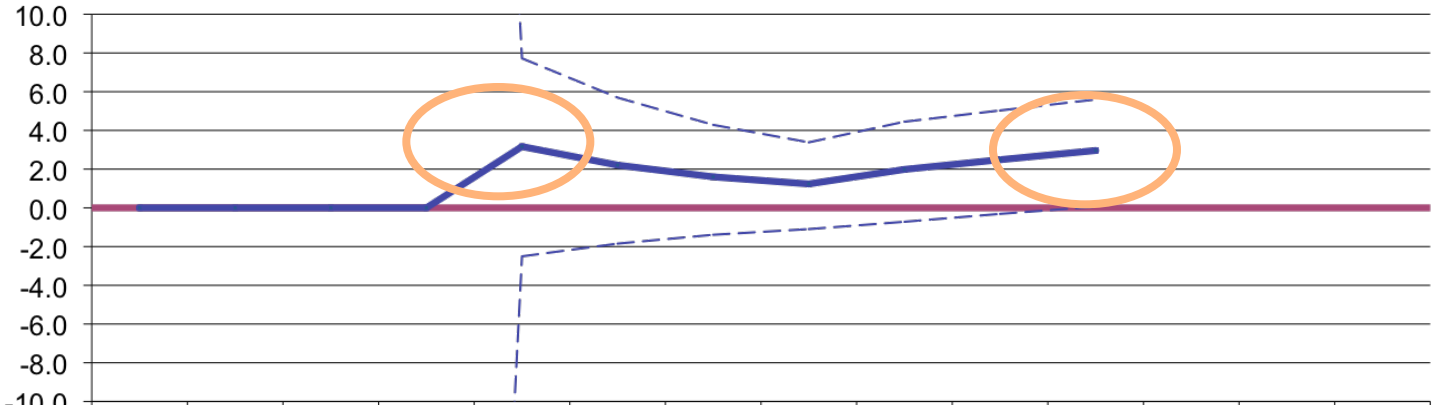
Monitoring for rhabdomyolysis:
cerivastatin (Baycol) vs. atorvastatin (Lipitor)



	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Lower 95% confidence interval	-99.00	-99.00	-99.00	-99.00	-2.50	-1.85	-1.39	-1.10	-0.72	-0.31				
Cumulative rate difference	0.00	0.00	0.00	0.00	3.17	2.21	1.60	1.24	1.99	2.49				
Upper 95% confidence interval	99.00	99.00	99.00	99.00	7.72	5.70	4.29	3.38	4.45	5.03				
Cumulative events: cerivastatin	0	0	0	0	1	1	1	1	2	3				
Cumulative events: atorvastatin	0	0	0	0	0	0	0	0	0	0				
Cumulative person-years cerivastatin	19	60	124	197	316	453	625	809	1007	1206				
Cumulative person-years: atorvastatin	26	65	127	218	348	497	681	877	1084	1299				

Gagne JJ et al. 2011

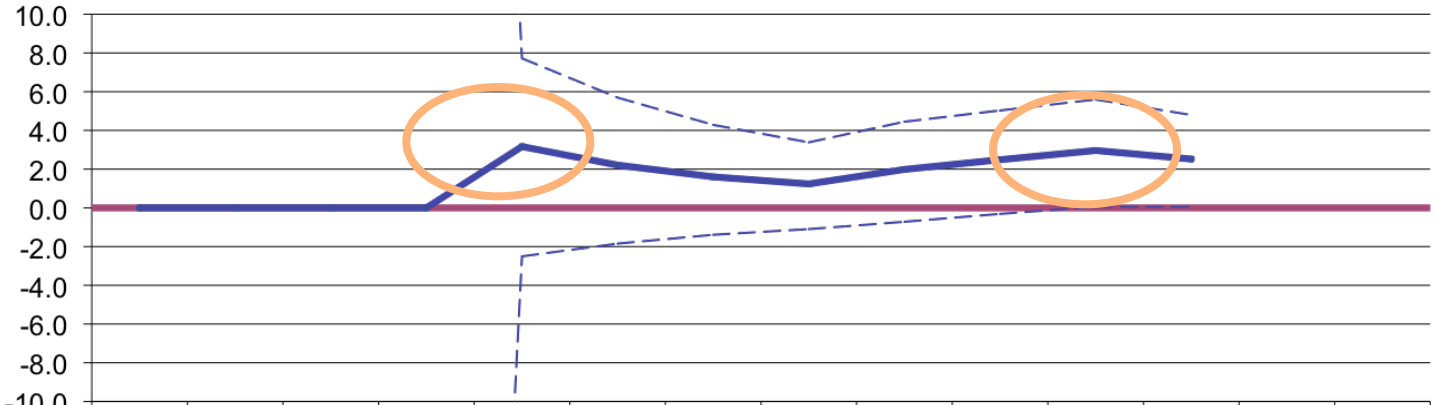
Monitoring for rhabdomyolysis:
cerivastatin (Baycol) vs. atorvastatin (Lipitor)



	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Lower 95% confidence interval	-99.00	-99.00	-99.00	-99.00	-2.50	-1.85	-1.39	-1.10	-0.72	-0.31	0.06			
Cumulative rate difference	0.00	0.00	0.00	0.00	3.17	2.21	1.60	1.24	1.99	2.49	2.96			
Upper 95% confidence interval	99.00	99.00	99.00	99.00	7.72	5.70	4.29	3.38	4.45	5.03	5.60			
Cumulative events: cerivastatin	0	0	0	0	1	1	1	1	2	3	4			
Cumulative events: atorvastatin	0	0	0	0	0	0	0	0	0	0	0			
Cumulative person-years cerivastatin	19	60	124	197	316	453	625	809	1007	1206	1350			
Cumulative person-years: atorvastatin	26	65	127	218	348	497	681	877	1084	1299	1462			

Gagne JJ et al. 2011

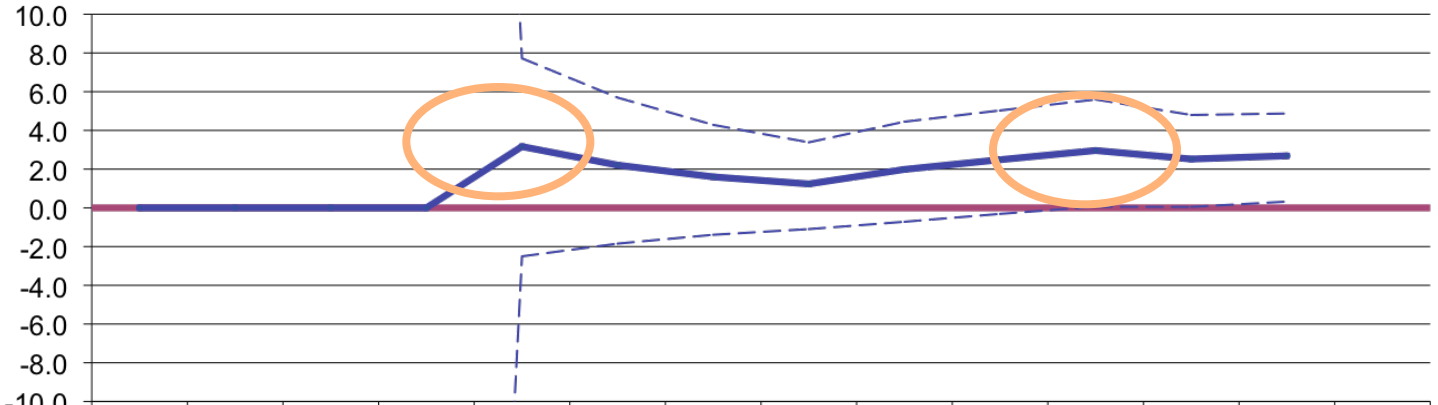
Monitoring for rhabdomyolysis:
cerivastatin (Baycol) vs. atorvastatin (Lipitor)



	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Lower 95% confidence interval	-99.00	-99.00	-99.00	-99.00	-2.50	-1.85	-1.39	-1.10	-0.72	-0.31	0.06	0.05		
Cumulative rate difference	0.00	0.00	0.00	0.00	3.17	2.21	1.60	1.24	1.99	2.49	2.96	2.52		
Upper 95% confidence interval	99.00	99.00	99.00	99.00	7.72	5.70	4.29	3.38	4.45	5.03	5.60	4.80		
Cumulative events: cerivastatin	0	0	0	0	1	1	1	1	2	3	4	4		
Cumulative events: atorvastatin	0	0	0	0	0	0	0	0	0	0	0	0		
Cumulative person-years cerivastatin	19	60	124	197	316	453	625	809	1007	1206	1350	1586		
Cumulative person-years: atorvastatin	26	65	127	218	348	497	681	877	1084	1299	1462	1715		

Gagne JJ et al. 2011

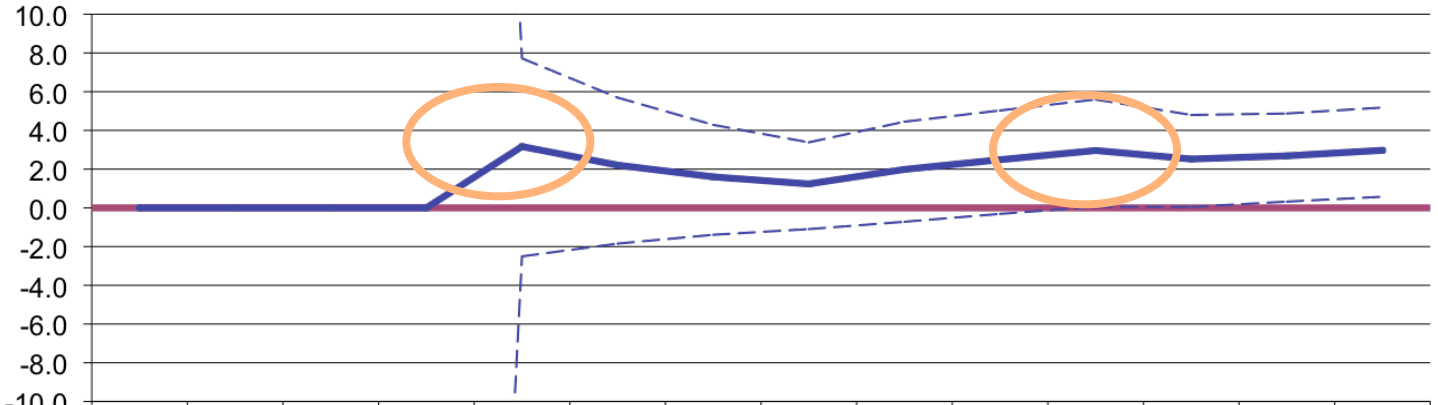
Monitoring for rhabdomyolysis:
cerivastatin (Baycol) vs. atorvastatin (Lipitor)



	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Lower 95% confidence interval	-99.00	-99.00	-99.00	-99.00	-2.50	-1.85	-1.39	-1.10	-0.72	-0.31	0.06	0.05	0.32	
Cumulative rate difference	0.00	0.00	0.00	0.00	3.17	2.21	1.60	1.24	1.99	2.49	2.96	2.52	2.69	
Upper 95% confidence interval	99.00	99.00	99.00	99.00	7.72	5.70	4.29	3.38	4.45	5.03	5.60	4.80	4.87	
Cumulative events: cerivastatin	0	0	0	0	1	1	1	1	2	3	4	4	5	
Cumulative events: atorvastatin	0	0	0	0	0	0	0	0	0	0	0	0	0	
Cumulative person-years cerivastatin	19	60	124	197	316	453	625	809	1007	1206	1350	1586	1861	
Cumulative person-years: atorvastatin	26	65	127	218	348	497	681	877	1084	1299	1462	1715	2010	

Gagne JJ et al. 2011

Monitoring for rhabdomyolysis:
cerivastatin (Baycol) vs. atorvastatin (Lipitor)



	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Lower 95% confidence interval	-99.00	-99.00	-99.00	-99.00	-2.50	-1.85	-1.39	-1.10	-0.72	-0.31	0.06	0.05	0.32	0.58
Cumulative rate difference	0.00	0.00	0.00	0.00	3.17	2.21	1.60	1.24	1.99	2.49	2.96	2.52	2.69	2.97
Upper 95% confidence interval	99.00	99.00	99.00	99.00	7.72	5.70	4.29	3.38	4.45	5.03	5.60	4.80	4.87	5.18
Cumulative events: cerivastatin	0	0	0	0	1	1	1	1	2	3	4	4	5	6
Cumulative events: atorvastatin	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cumulative person-years cerivastatin	19	60	124	197	316	453	625	809	1007	1206	1350	1586	1861	2019
Cumulative person-years: atorvastatin	26	65	127	218	348	497	681	877	1084	1299	1462	1715	2010	2275

Gagne JJ et al. 2011