Safety Signals with Blinded Data

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Statistical methodology has not been developed for safety monitoring to match that for efficacy monitoring.

Robert O'Neill (2002)

DMCs

Independent and separated from the ongoing collection and analysis of the data

Evaluate accumulating unblinded data

Make recommendations about the continuing safe conduct of the trial

Trial Leadership

Invested in the ongoing collection and analysis of data

Make the ethical decision about stopping the trial, when necessary

Could benefit from objective statistical rules that help them judge the strength of evidence contained in the blinded data

The idea for these safety signals originated from…

Peter Thall and Richard Simon
Practical Bayesian guidelines for Phase IIB clinical trials
Biometrics (1994) 50:337-349.

Likelihood Based Method

Bayesian framework

- Continuous safety monitoring
- Using all of the available information
- Without adjusting for multiple comparisons

Design Parameters

C = Critical rate

M = Minimum sample size

P = Probability threshold

N = Maximum sample size

- Determined by primary analysis

Null Rate

$R_0 \sim \text{Beta}(A, B)$

- Determined by M and C
- A + B = M
- A/(A + B) = C

Current Rate

$R \sim Beta(A + x, B + n - x)$

- Based on the accumulating data
- n pooled patients
- x events

Safety Signal

$$\text{Prob}(R > C \mid x) \geq P$$

If the probability that the current rate is greater than the critical rate, given the data, ever exceeds the probability threshold…

Then there's a signal

Designing Safety Signals

Collaborative effort

- Pharmacovigilance
- Medical Science
- Statistics

Simulations show the operating characteristics

- Computationally intensive
- Iterative process
- No need to quantify prior opinion
- Implementation is easy

Good Operating Characteristics

Trials that should stop

- High probability of a signal
- Small median sample size

Trials that should continue

- Low probability of a signal
- Large median sample size

Greg Ball, Linda B Piller and Michael H Silverman
Continuous safety monitoring for randomized controlled clinical trials with blinded treatment information
Contemporary Clinical Trials (2011) 32:S1-S17.

Neutrophil Count < 2000

Study 1

Full Sample Size = 275

4 Active : 1 Placebo

Operating Characteristics of Signal for Neutrophil Count < 2000 in Study 1
Signal if Probability (Rate > C | data) ≥ P
C = 0.066, M = 50, P = 0.80

True Rates			Percentage of Trials with an Early Signal	Sample Size at 1st Signal		
Placebo Group	Active Dose Groups	Pooled Data		1st Quartile	Median	3rd Quartile
0.00		0.032	1.0	275	275	275
0.01	0.04	0.034	1.4	275	275	275
0.02		0.036	1.9	275	275	275
0.00		0.048	8.5	275	275	275
0.01	0.06	0.050	10.4	275	275	275
0.02		0.052	12.7	275	275	275
0.00		0.064	32.6	155	275	275
0.01	0.08	0.066	36.9	130	275	275
0.02		0.068	41.3	105	275	275
0.00		0.080	67.4	60	145	275
0.01	0.10	0.082	70.9	60	130	275
0.02		0.084	74.2	55	115	275

C = Critical Rate, M = Minimum Sample Size, P = Probability Threshold
Full Sample Size = 275
10,000 Simulations

Neutrophil Count < 2000

Studies 1 and 2 Combined

Full Sample Size = 650

4 Active : 1 Placebo

Operating Characteristics of Signal for Neutrophil Count < 2000 in Both Studies
Signal if Probability (Rate > C | data) ≥ P
C = 0.066, M = 100, P = 0.80

True Rates			Percentage of Trials with an Early Signal	Sample Size at 1st Signal		
Placebo Group	Active Dose Groups	Pooled Data		1st Quartile	Median	3rd Quartile
0.00		0.032	0.2	650	650	650
0.01	0.04	0.034	0.4	650	650	650
0.02		0.036	0.6	650	650	650
0.00		0.048	4.8	650	650	650
0.01	0.06	0.050	6.5	650	650	650
0.02		0.052	8.9	650	650	650
0.00		0.064	34.8	280	650	650
0.01	0.08	0.066	41.4	220	650	650
0.02		0.068	48.0	180	650	650
0.00		0.080	83.5	100	195	450
0.01	0.10	0.082	87.2	100	180	385
0.02		0.084	90.2	100	155	335

C = Critical Rate, M = Minimum Sample Size, P = Probability Threshold
Full Sample Size = 650
10,000 Simulations

Safety Signal Calculator

C =	6.6%	Rate =	10.0%
M =	100	n =	100
P =	0.80	x =	10
Probability =		0.805	

Safety Signal Calculator

C =	6.6%	Rate =	10.0%
M =	100	n =	200
P =	0.80	x =	20
Probability =		0.926	

Safety Signal Calculator

C =	6.6%	Rate =	9.0%
M =	100	n =	200
P =	0.80	x =	18
Probability =		0.846	

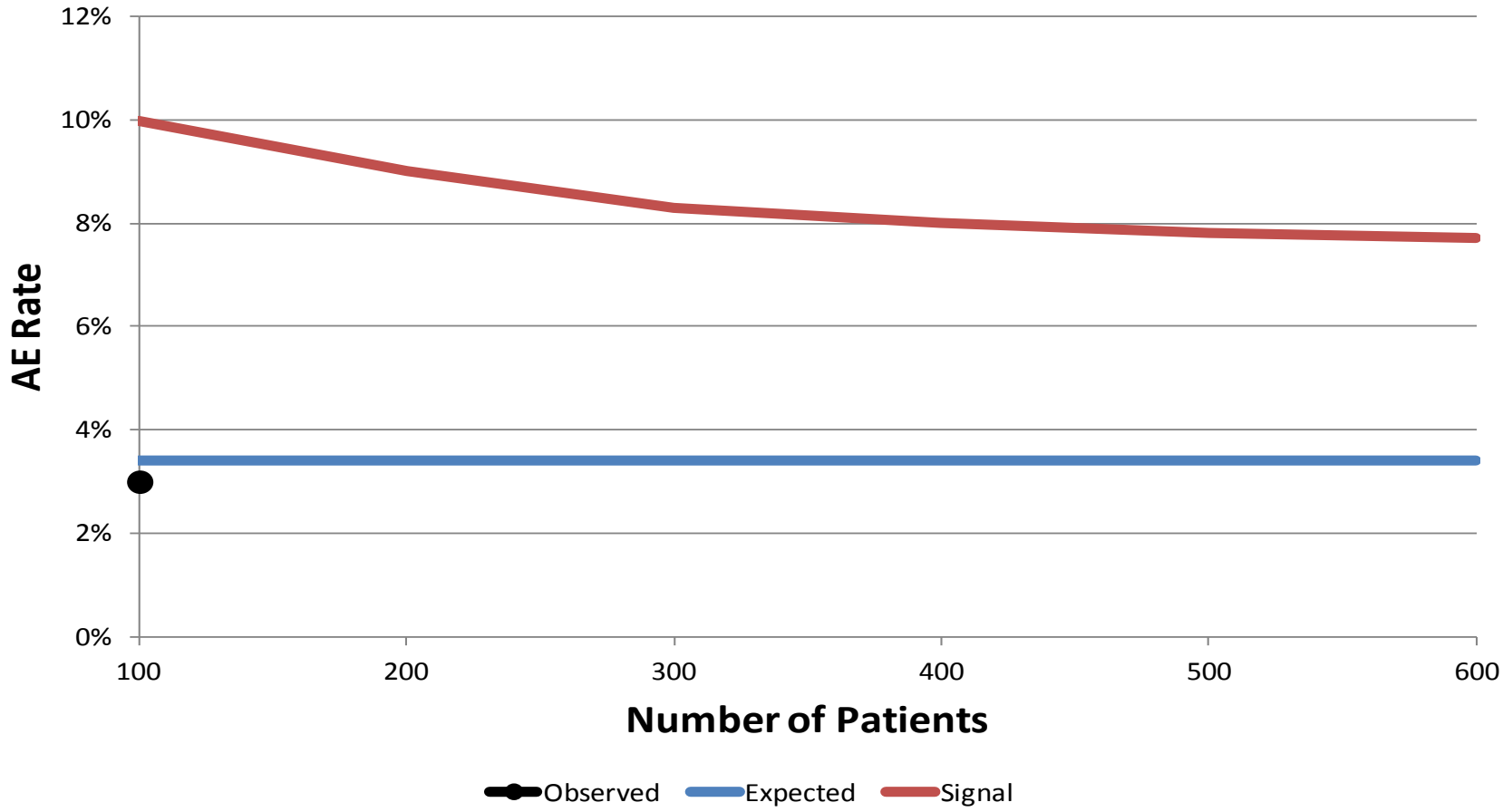
Safety Signal Calculator

C =	6.6%	Rate =	8.0%
M =	100	n =	400
P =	0.80	x =	32
Probability =		0.825	

Safety Signal Calculator

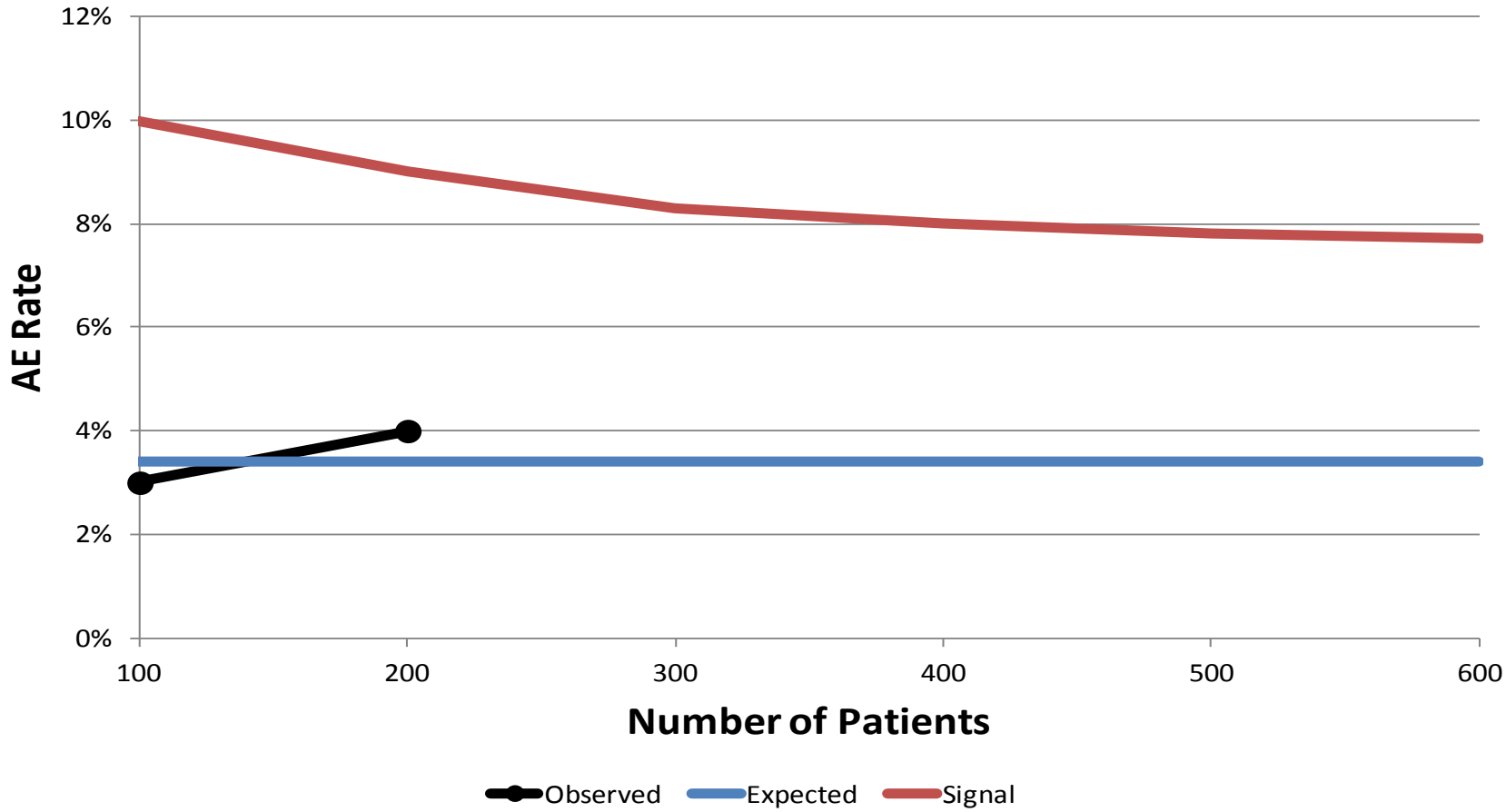
C =	6.6%	Rate =	7.7%
M =	100	n =	600
P =	0.80	x =	46
Probability =		0.819	

Signal for Neutrophil Count < 2000
Studies 1 and 2 Combined

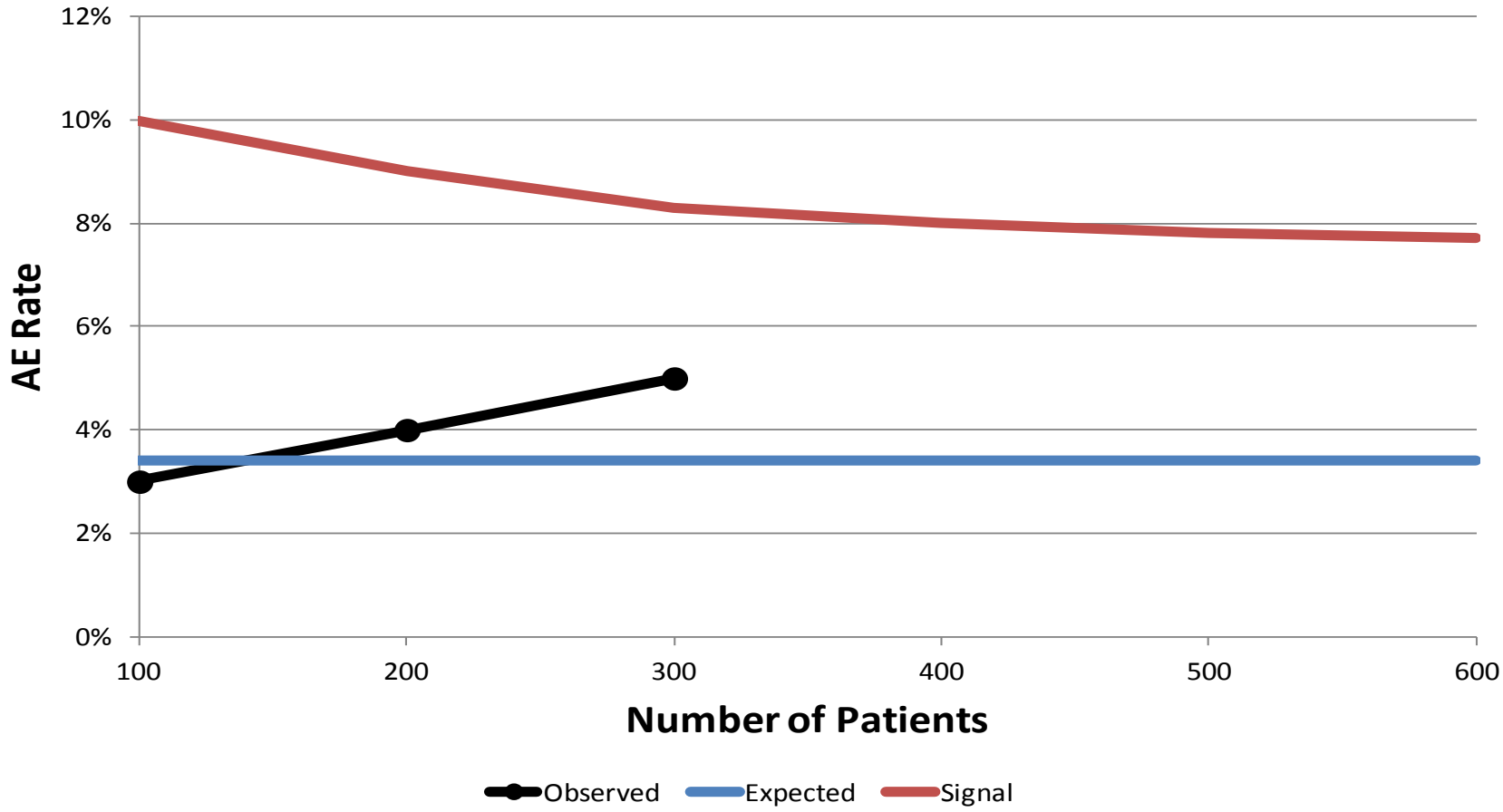


Changing tomorrow

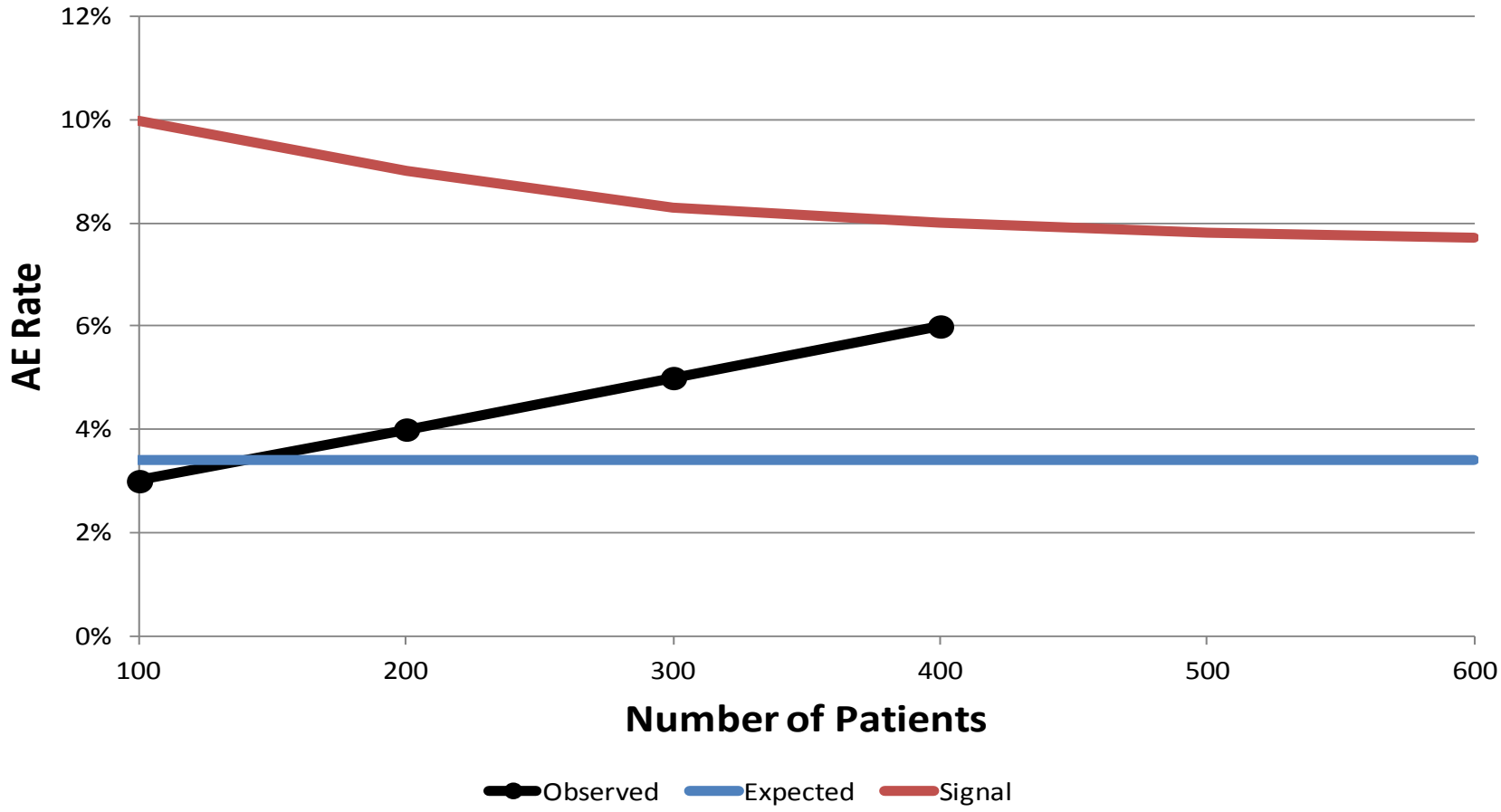
Signal for Neutrophil Count < 2000
Studies 1 and 2 Combined



Signal for Neutrophil Count < 2000
Studies 1 and 2 Combined



Signal for Neutrophil Count < 2000
Studies 1 and 2 Combined



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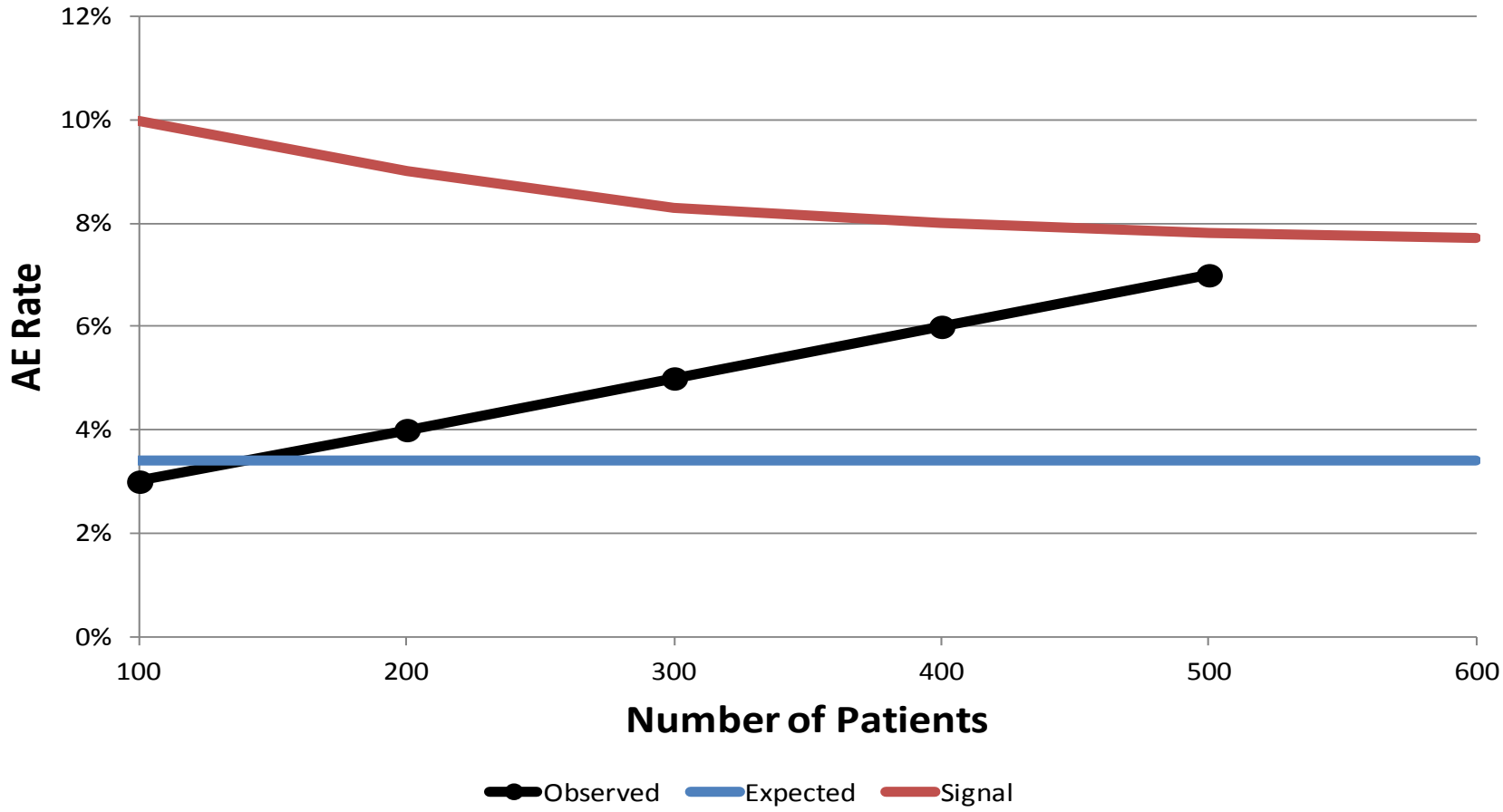
Studies 1 and 2 Combined



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Signal for Neutrophil Count < 2000
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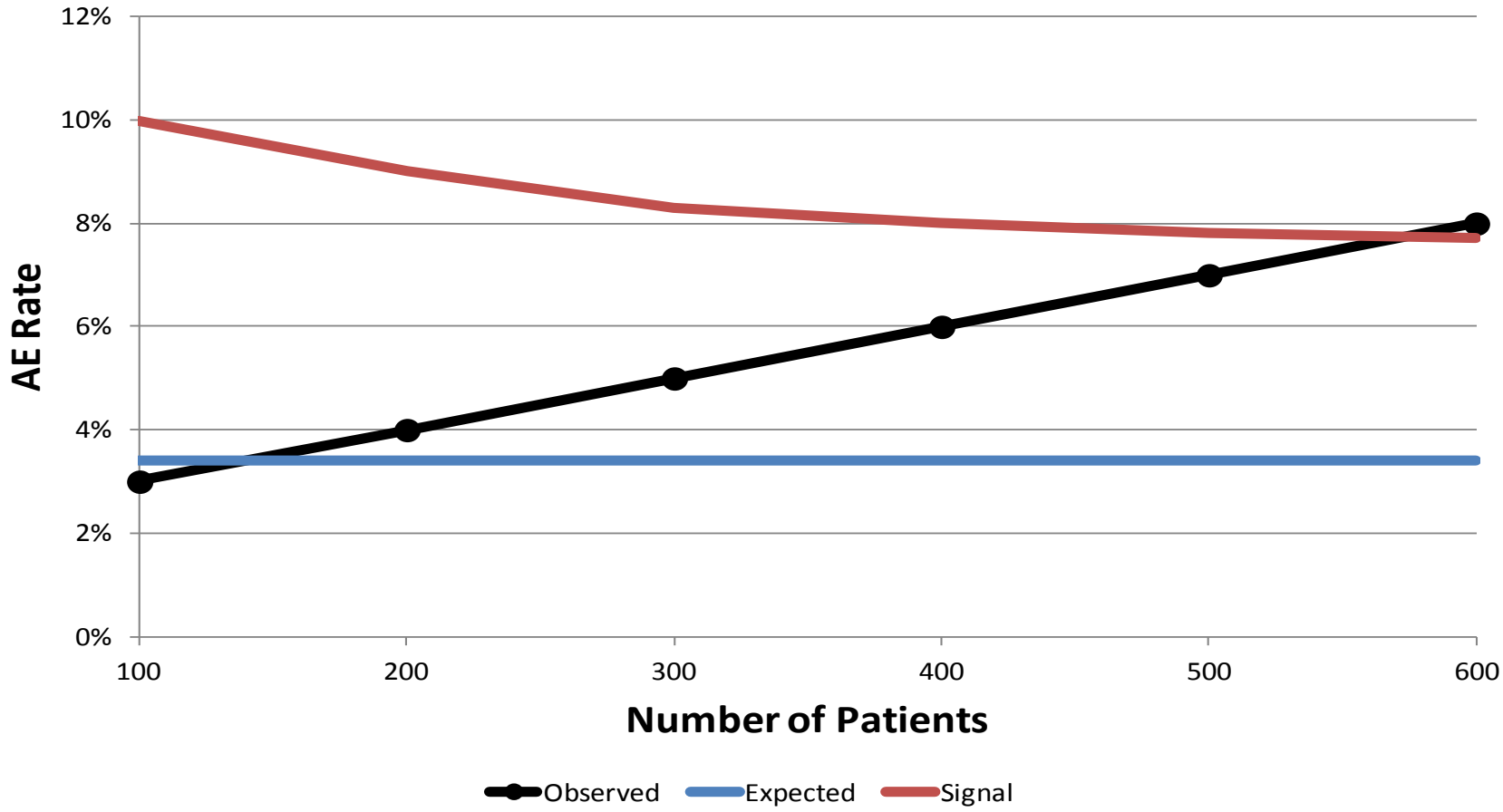

Conclusion 1 of 2

It is imperative that emerging trends in the data are frequently and carefully evaluated to protect the safety and welfare of patients. While trial leadership must conscientiously maintain their blind, DMCs must have unblinded access to all of the available information, so that together they can fully protect patients from unsafe treatments, without compromising trial integrity or otherwise interfering with the strength of evidence.

Conclusion 2 of 2

Safety signals will provide a full measure of the blinded data that the trial leadership can use, in combination with open information from the DMC, to evaluate the strength of evidence in the available data in order to make fully informed decisions that protect patients from unnecessary harm while allowing the trials to lead to conclusive results.