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ROBUST SAFETY MONITORING AND SIGNAL DETECTION USING ALTERNATIVES TO THE STANDARD POISSON DISTRIBUTION

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Robust Safety Monitoring and Signal Detection Using Alternatives to the Standard Poisson Distribution

Abstract:

Proper and timely characterization of the safety profile of a pharmaceutical product under development, is imperative for assessing the overall benefit-risk relationship of the product, and for making key development decisions. For ongoing clinical development, a comprehensive and robust safety monitoring and safety signal detection (SSD) program which is based upon inferential statistical reasoning is critical. Methods presented here can be applied to SSD as well as periodic safety monitoring (e.g., SUSAR reporting, Development Safety Update Report [DSUR], Investigator Brochure IB], etc.). Various statistical properties, distributions, and models, utilizing a Bayesian framework are considered and further examined, to identify robust methods applicable to a broad set of scenarios and situations. Methods developed for incidence counts (including those with under-dispersed distributions) with variable time-at-risk, and with underlying constant or non-constant hazard rates, are proposed and compared to traditional methods designed to assess adverse event incidence rates or binomial incidence proportions, which assume an underlying constant hazard rate and subsequent Poisson distribution for modeling event counts.

Agenda / Outline

Motivation for Safety Signal Detection (SSD)

- Regulatory requirements / Sponsor obligations
- Traditional monitoring processes/methods
- Recent methodology
- Expansions to traditional and recent methodologies

Robust Signal detection: for clinical trials data

- Objectives of SSD blinded analyses
- Theoretical considerations
- Models evaluated
- Simulation methods
- Results / Discussion / Summary
- SSD Visualization
- SSD and IND Safety Reporting

Lessons Learned / Final Thoughts / Conclusion

- Additional research and next steps
- Lessons learned / Final thoughts

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Motivation for Safety Signal Detection (SSD)

Motivation for SSD

- **Pharma in the news**

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Monday, July 2, 2012

[redacted] to Plead Guilty and Pay $3 Billion to Resolve Fraud Allegations and Failure to Report Safety Data

Largest Health Care Fraud Settlement in U.S. History

Global health care giant [redacted] agreed to plead guilty and to pay $3 billion to resolve its criminal and civil liability arising from the company's unlawful promotion of certain prescription drugs, its failure to report certain safety data, and its civil liability for alleged false price reporting practices, the Justice Department announced today. The resolution is the largest health care fraud settlement in U.S. history and the largest payment ever by a drug company.

Regulatory requirements / Sponsor obligations

➢ Regulatory Environment

- Code of Federal Regulations (CFR 312.32)
- Safety Reporting Requirements for INDs and BA/BE Studies (Final Guidance, Dec 2012)
  - An "aggregate analysis of specific events observed in clinical trials that indicate those events occur more frequently in the drug treatment group than in a concurrent or historical control group"
- Safety Assessment for IND Safety Reporting (Draft Guidance for Industry, Dec 2015)
  - Sponsors should develop a Safety Assessment Committee and a Safety Surveillance Plan.
  - Sponsors should periodically review accumulating safety data, integrated across multiple completed and ongoing studies
  - Provide a quantitative framework for measuring the evidence of an association (unexpected events) or a clinically important increase (for expected events)
- Sponsor Responsibilities – Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies (Draft Guidance 2021)

Regulatory requirements / Sponsor obligations

➢ Regulatory Environment

Safety Monitoring and SSD requirements (regulatory)

- **Signal Definition**
  Information that arises from one or more multiple sources (including observations or **experiments**), which suggests a new, potentially **causal association**, or a new aspect of a known association between an intervention [e.g., administration of a medicine] and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action. *(CIOMS, 2010, p. 14)*

- **Signal Detection Definition**

  The act of looking for and/or identifying signals using event data from any source. *(CIOMS, 2010, p. 116)*

- **The Core of Safety Signal Detection**

  Define and assess measures of disproportionate reporting (e.g. observed / expected). Identify events exceeding a specified threshold. *(Good Pharmacovigilance Practices…, 2005)*

Regulatory Requirements / Sponsor obligations

Commitment to Patient Safety

- "Patient safety is at the heart of all we do and one of our core principles. All of our medicines undergo thorough safety monitoring and evaluation processes at every stage of a medicine's lifecycle" – Teva Pharmaceuticals
- "Mallinckrodt is committed to the safety of patients, including those in the hospital settings, and the safe use of our broad portfolio of specialty pharmaceutical products," – Hugh O'Neill, Sr. VP and President, U.S. Specialty Pharmaceuticals, Mallinckrodt.
- "Beginning with the discovery of a potential new medicine, and for as long as it is available to patients, our goal is to ensure that the benefits and risks of a medication are continuously monitored and well-understood by regulators, healthcare providers and patients." – Eli Lilly
- "Part of our responsibility as a global pharmaceutical company is to help keep the patients who take our medicines safe." – Pfizer
- "Celgene is a world leader in pioneering risk minimization techniques to deliver safe use of medicinal products." – Celgene
- "Patient safety is the top priority for Biogen and AbbVie".

Regulatory Requirements / Sponsor obligations

➢ Corporate Principles and Values

- ❑ Accurate characterization of a compound's safety profile is essential:
  - Patient safety
  - Valuation of compound
  - Required to provide timely and accurate information on informed consent (IC) statements and investigator brochures (IB).
  - Aggregated data across all trials is required.

- ❑ Failure to report all safety findings in a timely manner leads to injury, loss of life, loss of consumer confidence for the company / industry, as well as significant financial implications for the company.

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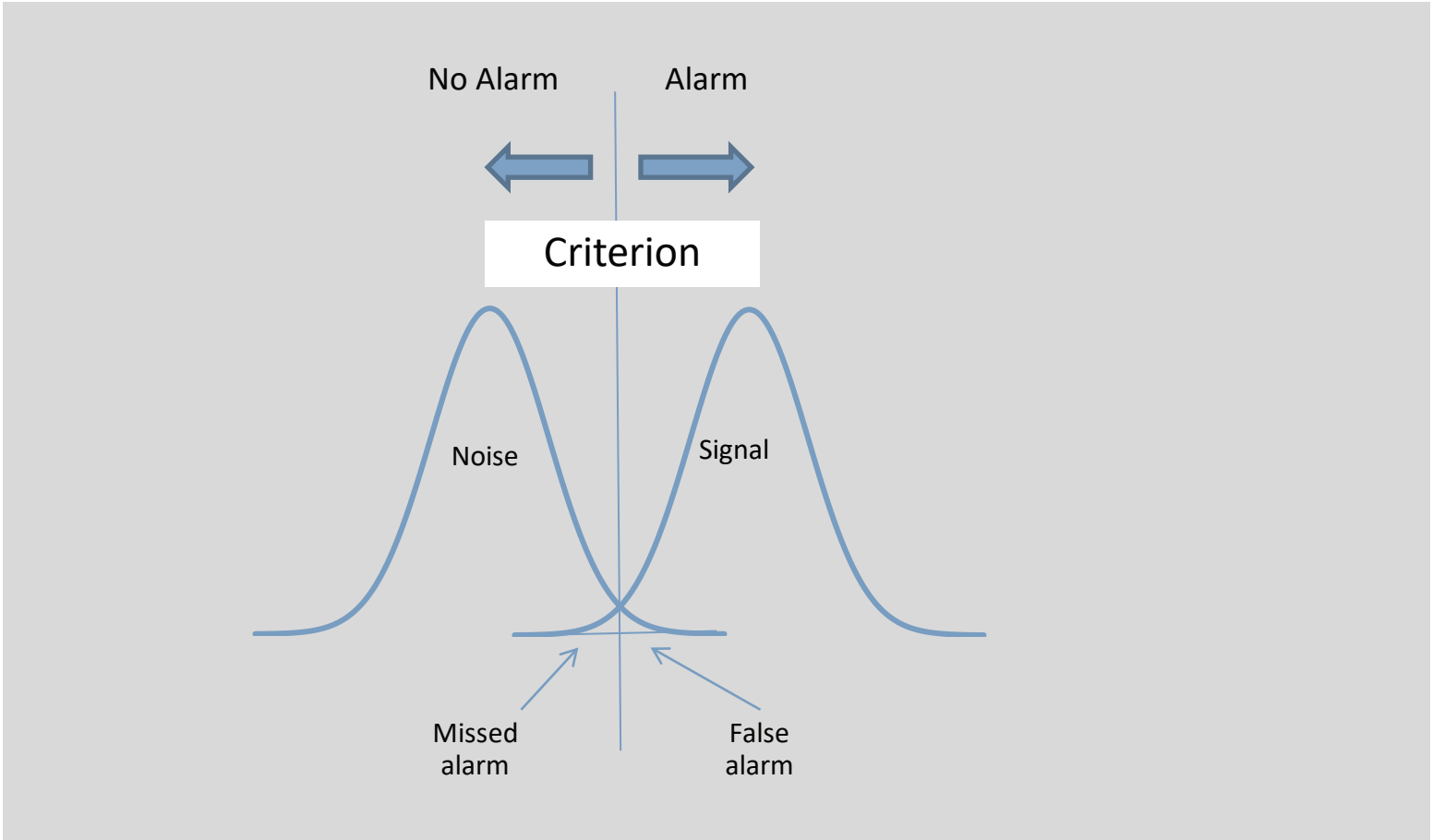
Robust Signal Detection: for Clinical Trials Data

Objectives of SSD Blinded Analyses

- Research for blinded analyses, Findings, and Results



Objectives of SSD Blinded Analysis

- Core Question

An Example:

- Assume that the underlying AE pbo inc. prop. for a significant event (estimated from historical data (n=500) with 24 weeks of follow-up) is 2%.

- A new blinded study has Y events after 80 subjects (3:1 randomization ratio) have completed 24 weeks.

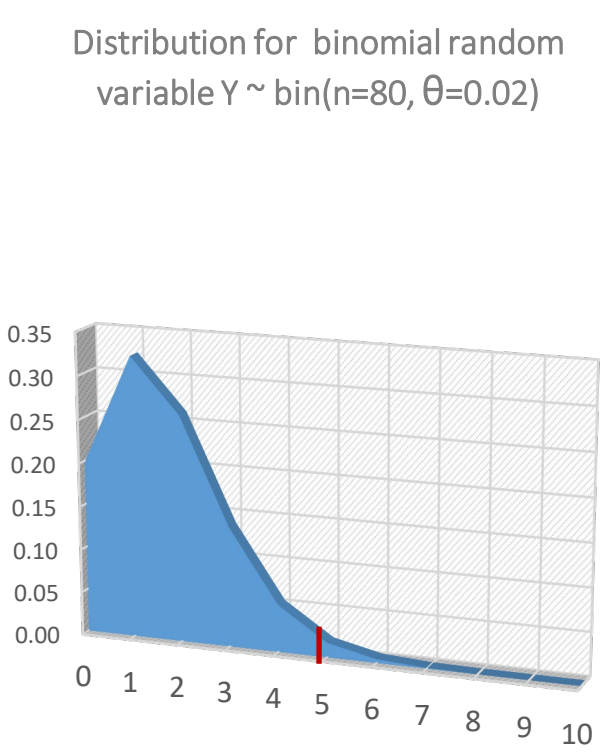
- What is the expected value of Y, if there is no difference between actively treated subjects and current and historical placebo? How large does Y have to be to suggest that a difference (i.e. “signal”) exists?

Theoretical Considerations: Simple example

➢ A Simple Frequentist Solution

Binomial Distribution

- pmf: $p(y) = \binom{n}{y} \theta^y (1-\theta)^{n-y}$, $y=0,1,2,\ldots,n$
- $E(Y_i) = \theta$, $var(Y_i) = \theta(1-\theta)$
- Y is a binomial random variable with mean and variance:
  - $\mu = E(Y) = n\theta$
  - $\sigma^2 = var(Y) = n\theta(1-\theta)$
  - Expected value: $n\theta = (80)(.02) = 1.6$



n = 80, θ = 0.02

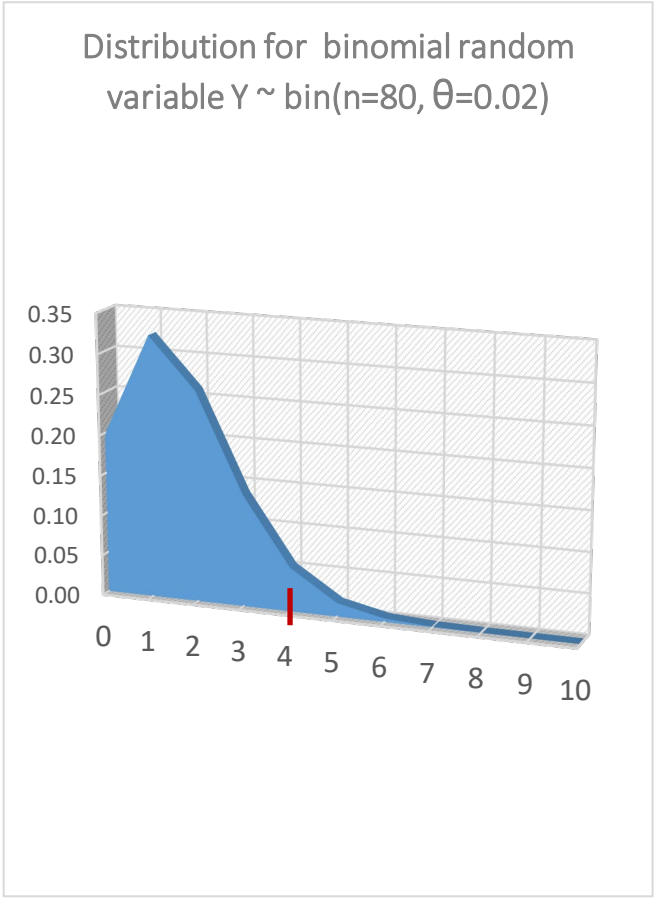
	Probability	
P(Y < y)	Binomial	Poisson
1	0.1986	0.1986
2	0.5230	0.5197
3	0.7844	0.7792
4	0.9231	0.9189
5	0.9776	0.9754
6	0.9946	0.9986
7	0.9989	0.9997

Theoretical Considerations: Simple example

➢ A Simple Frequentist Solution: Additional Questions

Questions \ Issues

- How did we derive our estimate for θ?
- How confident are we in our value of θ?
- What if our time-at-risk for our new blinded data is not equal to our time-at-risk from our historical data?
- What if subjects have varying follow-up time?
- What if our rates are not small?
- What if our underlying risk is variable (e.g., non-constant hazard rate)?
- What if our historical population is not representative of our new study population(s)?



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1	0.1986
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5	0.9776
6	0.9946
7	0.9989

Theoretical Considerations: Bayesian refresher

➢ Bayesian Philosophy, Bayes' Theorem and Bayesian Analysis

❑ Bayesian Philosophy

- Bayes' rule provides a rational method for updating beliefs in light of new information (inductive learning ~ Bayesian inference)
- Bayesian methods are data analysis tools derived from the principles of Bayesian inference
- Statistical induction is the process of learning about the general characteristics of a population from a subset of members of that population.

❑ Bayes' Formula/Theorem

- P(A/B) = P(BA) / P(B) = [P(B/A)P(A)] / [P(B/A)P(A) + P(B/$\overline{A}$) P($\overline{A}$)]
- $p(\theta|y) = \frac{p(y/\theta)p(\theta)}{\int_{\Theta} p(y/\tilde{\theta})p(\tilde{\theta})d\tilde{\theta}}$

Theoretical Considerations: Bayesian refresher

- Bayesian Philosophy, Bayes' Theorem and Bayesian Analysis

In Bayesian Analysis

– $P(\theta|y) \propto P(y|\theta)\,P(\theta)$

Likelihood model

Prior Distribution

Posterior Probability

- The sample space Y is the set of all possible datasets, from which a single dataset y (the observed data) will result.
- The parameter space Θ is the set of possible parameter values, from which we hope to identify the value that best represents the true population characteristics.
- The prior distribution p(θ) describes our belief that θ represents the true population characteristic (e.g. our historical data).
- The sampling model for the data p(y|θ) describes our belief that y would be the outcome of our study if we knew θ to be true.
- Once the data (y) is obtained, we update our beliefs about θ. Therefore our posterior distribution p(θ/y) describes our belief that θ is the true value, having observed dataset y.

Theoretical Considerations: Mixture models

➢ The Form of the Finite Mixture Model

❑ Model description and specifications

- Suppose you observe realizations of a random variable Y, in which the distribution depends on an unobservable (latent) random variable S (e.g. treatment group assignment) that has a discrete distribution and can occupy one of k states (e.g. placebo, active treatment).
- Let π_j denote the probability that S takes on state j. Conditional on S = j, Y is assumed to be $f_j(y; S=j)$.
- The marginal distribution of Y is obtained by summing the joint distribution of Y and S over the states in the support of S:
  - $f(y;\alpha,\beta) = \sum_{j=1}^{k} \Pr(S = j)\, f(y; \alpha_j, \beta_j|S) = \sum_{j=1}^{k} \pi_j\, f(y; \alpha_j, \beta_j|S=j)$
  - This is a mixture of distributions and the π_j are called the mixture (or prior) probabilities.
  - This model is termed a Finite Mixture (of distributions) model, because there are k finite states of S.
  - For categorical data, the binomial and beta-binomial distributions can be specified for the data.

Theoretical Considerations: Bayesian Application to SSD

➢ General Bayesian Framework for assessing safety signals

Framework that applies to all models

- The Bayesian framework for potential signal detection is based on evaluating the probability that a clinical parameter of interest (e.g. adverse event incidence rate or proportion) exceeds a pre-specified critical value, given the observed blinded data. Mathematically, this is formulated as an inequality around a threshold and corresponding Bayesian posterior probability and is denoted as (Wen et al., 2015):
  - **$Pr(\theta > \theta_c \mid$ blinded observed data$) >$ *P* cut-off**

where: θ represents the clinical parameter of interest(e.g., "pooled blinded proportion", estimated risk difference, etc.)

θ_c represents the critical value for comparison (e.g., historical incidence proportion, or 0 if estimated risk difference is the clinical parameter of interest),

P cut-off is a probability threshold (such as 90%, 95%, or 99%) representing the desired confidence needed to identify a potential safety signal.

Theoretical Considerations: Distribution Relationships

➢ Exponential, Binomial, Poisson, Gamma

❑ Exponential → Poisson

- If the times between random events follow the exponential distribution with rate λ, then the total number of events in a time period of length t follows the Poisson distribution with parameter λt.
- Interarrival times are independent and identically distributed exponential (λ) random variables, when λ is the rate of the Poisson process

❑ Poisson → Binomial/Bernoulli

- If we divide an interval of time into disjoint intervals of length h, where h is small [e.g. 0 –h, h-2h, 2h-3h,…], each interval corresponds to an independent Bernoulli trial, such that in each interval, there is a successful event with prob. λh.
- Bernoulli process is a discrete time approximation to the Poisson process with rate λ, if the distribution of B(t) is approximately Poisson (λt)

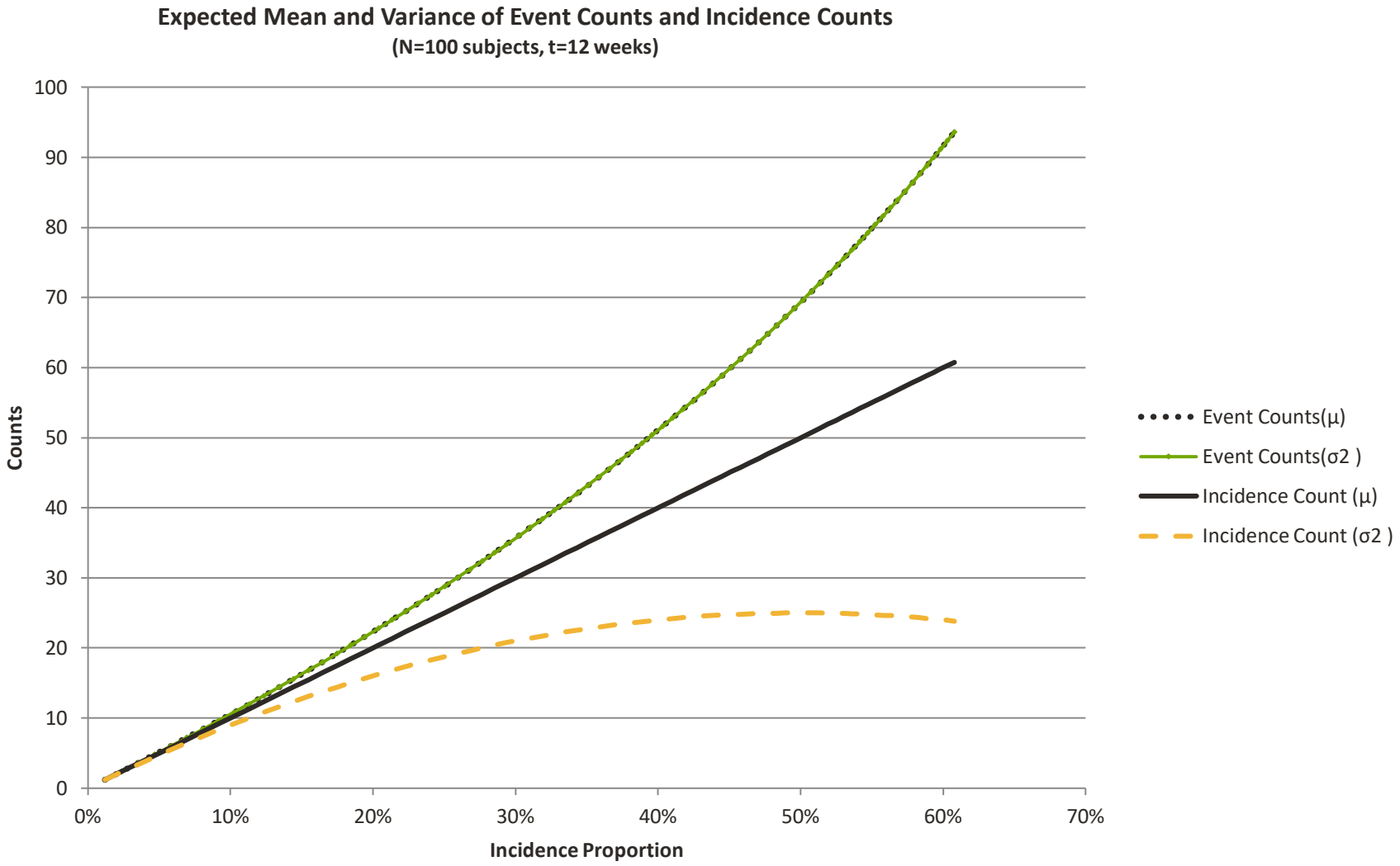
❑ Poisson → Gamma

- Time until nth event occurs has a Gamma (n, λ) distribution

Theoretical Considerations: Event counts vs incidence counts

- Event Counts
  - The Poisson distribution is a reasonable model for event counts if the event can happen more than one time.
    - One parameter model with equal mean and variance.
    - Assumes time to each event has an underlying constant hazard rate.
    - Commonly used to model adverse events
- Incidence Counts
  - Number of subjects who experience one or more of the given event (only 1st occurrence of event within a subject is considered); this is the typical parameter summarized/analyzed.
    - This subtle restriction is sometimes ignored/overlooked
    - More adequately described as grouped binary data (i.e., Bernoulli trials).
    - Can lead to under-dispersed distribution (variance < mean)

Theoretical Considerations: Event counts vs incidence counts



Theoretical Considerations: Subject Follow-up time / time-at-risk

- Subject Follow-up Time
  - Follow-up time will vary from just a few days to several years due to premature withdrawal, interim looks, etc.
    - With event counts (using the Poisson distribution) varying time among subjects does not matter.
    - With incidence counts varying time among subjects can matter

- Example

λ (per week) =		***0.0250***			
Inter-event time (1/λ) =		***40***			
	Scenario (1)			**Scenario (2)**	
Subject	**Time (w)**	**Prob(Event)**		**Time (w)**	**Prob(Event)**
1	24	0.4512		2	0.0488
2	24	0.4512		16	0.3297
3	24	0.4512		24	0.4512
4	24	0.4512		36	0.5934
5	24	0.4512		42	0.6501
Totals (Expected Counts):					
Incidence	120	**2.26**		120	**2.07**
Events (λt) =	120	3.00		120	3.00

Models Evaluated: Constant Hazard Rate

- **Poisson[BDRIBs (1) and (2)] – Poisson likelihood**
  - Model (1A) [Poisson (1)]: All (total) exposure time used in calculations

Model (1A): Poisson(1) [BDRIBs]: $Y \mid E, \delta_{HP}, k, r \sim Poisson(\lambda)$
where: $\lambda = E * \delta_{HP} * [(r * k + 1)/(k + 1)]$
E = Total exposure time (for total blinded population)
$\delta_{HP} \sim Gamma(\alpha_{HP}=[\lambda_{HP} x\ PT_{HP},]/DF, \beta_p = PT_{HP}/DF)$
k = Randomization allocation ratio
r = $p / [k(1 – p)]$, relative risk ratio of test (drug) treatment over placebo
$p \sim Beta(0.5, 0.5)$ [default non-informative prior for p]
DF = Discount Factor

  - Model (1B) [Poisson (2)]: Time-at-risk exposure time used in calculations

Model (1B): Poisson[BDRIBs]
E = Total time at risk (for total blinded population). All other information is identical to Model 1A.

Models Evaluated: Constant Hazard Rate

- **Exponential Bernoulli (EXP_BERN) – Right-censored(1) Poisson likelihood**
  - Model (2) [EXP_BERN]
    - Incidence count in which events arrive from a Poisson distribution can be modeled with a right-censored(1) Poisson distribution (i.e., all event counts within a subject greater than 1 are re-valued to 1).

$f(y_i; \lambda t_i) =$	$(1 - e^{-\lambda t[i]})^{y[i]} (e^{-\lambda t[i]})^{\{1 - y[i]\}}$;	$x_i = 0, 1$

    - As seen above, the formula is a Bernoulli distribution in which the probability of an event is derived from the relationship between the Poisson and exponential distribution. The model is parameterized as follows:

Model (2): EXP_BERN: $Y_i \mid \lambda_p, r, k, t_i \sim$ Mixture Bernoulli(π_{pti}, π_{dti},) ; i=1,…,N
where: $\pi_{pti} = 1 - \exp[-\lambda_p(t_i)]$, and $\pi_{dti} = 1 - \exp[-r\lambda_p(t_i)]$
$\lambda_p \sim$ Gamma(α_p=[λ_{HP} x PT_{HP}]/DF, $\beta_p = PT_{HP}$/DF}
r = p /k(1-p), relative risk ratio of test (drug) treatment over placebo
k = Randomization allocation ratio
p ~ Beta(0.5, 0.5)
t_i represents the follow-up time for patient I; DF = Discount Factor

  - Model (1B) [Poisson (2)]: Time-at-risk exposure time used in calculations

Models Evaluated: Non-constant Hazard Rate

- **Log-logistic Bernoulli (LL_BERN)**
  - Model (3) [LL_BERN]
    - Incidence count in which events arrive from underlying non-constant hazard rates can be modeled with a log-logistic distribution. The model is parameterized as follows:

Model (3): LL_BERN: $Y_i \mid \mu_p, \mu_d, \sigma_p, \sigma_d, t_i \sim$ Mixture Bernoulli$(\pi_{pti}, \pi_{dti},)$; $i=1,\ldots,N$
where: $\pi_{pti} = 1 - 1 / [1 + \exp((\ln(t_i) - \mu_p)/ \sigma_p)]$; $i = 1,\ldots,N$
$\pi_{dti} = 1 - 1 / [1 + \exp((\ln(t_i) - \mu_d)/ \sigma_d)]$; $i = 1,\ldots,N$
$\mu_p \sim$ Gamma$(\alpha = a/DF_p, \beta = PT_{HP}/DF_p)$
$\mu_d \sim$ Gamma$(\alpha = a/DF_d, \beta = PT_{HP}/DF_d)$
$\sigma_p \sim$ Gamma $(\alpha = b/DF_p, \beta = PT_{HP}/DF_p)$
$\sigma_d \sim$ Gamma $(\alpha = b/DF_d, \beta = PT_{HP}/DF_d)$
t_i represents the follow-up time for patient i.
DF = Discount Factor

Models Evaluated: Summary

- Table of models investigated

Model Number	Model Name	Priors	Likelihood (data) model	HR Assumption
Model 1A	Poisson(1) [bdribs]	PBO rate (δ_{HP}) ~ Gamma; Rate Ratio ~ Beta	Poisson	Constant
Model 1B	Poisson(2) [modified bdribs – exposure time]	PBO rate (δ_{HP}) ~ Gamma; Rate Ratio ~ Beta	Poisson	Constant
Model 2	EXP_BERN	PBO rate (λ_P) ~ Gamma; Rate Ratio ~ Beta	Exponential-Bernoulli	Constant
Model 3	LL_BERN	PBO rate (μ_p, σ_p) ~ Gamma DRG rate (μ_d σ_d) ~ Gamma	Log-logistic-Bernoulli	Non-constant

Models Evaluated (simple example)

➢ Core Question Re-visited (slightly modified)

Obs. Data:

N = 80

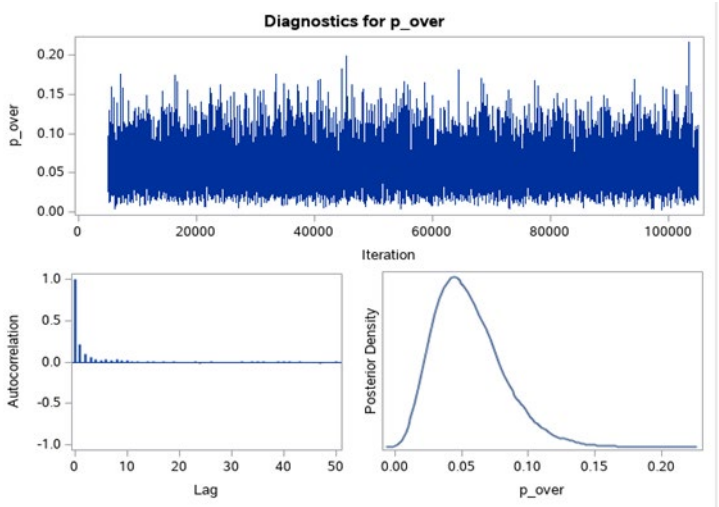
(but with variable follow-up time (1.6 – 24 weeks)

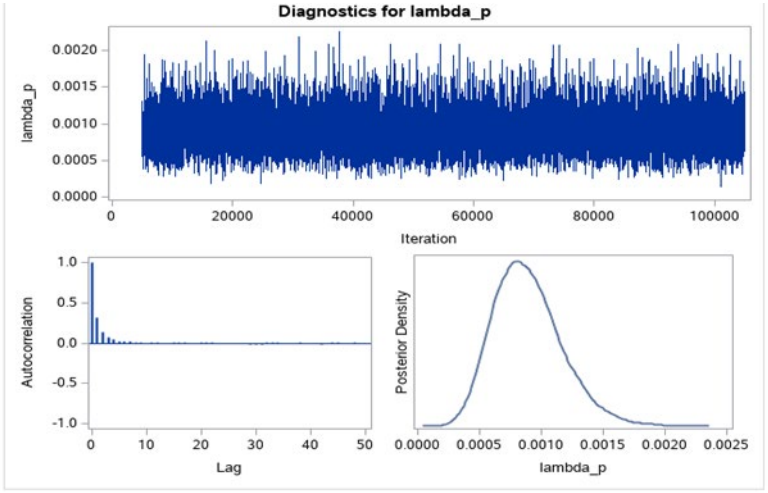
Observed events = 5

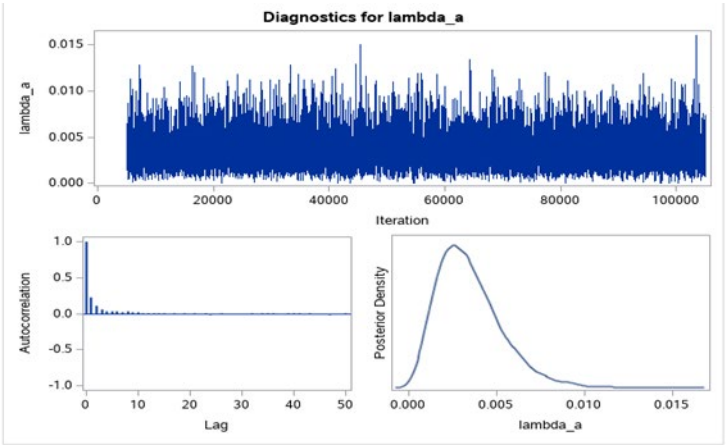
$P(\theta > \theta c \mid Y) = 0.9527$ (where θ = RR, $\theta c = 1$)

From Bayesian Exponential-Bernoulli model

(allows for variable follow-up)







Simulation Methods

➢ Objectives and Data Creation Methods

Objective of Simulations

- ❑ Compare the various methods for efficiency and estimation accuracy
  - Assess the sensitivity (power) and specificity (false positives) of the methods
  - Compare estimates obtained from each model to expected values (e.g. underlying means specified in the simulated data)

Data Creation Methods Overview

- ❑ Simulated time to adverse event
  - Constant HR: (Weibull distribution with shape parameter= 1 ~ Exponential Distribution])
  - Non-constant HR: (Log-logistic Distribution)
- ❑ Simulated enrollment of patients using the Uniform distribution
  - Allowed for simulation of separate interim SSD cuts in which patients, time-at-risk and events accrued over time.
- ❑ Simulated variable event rates, treatment effects, sample size, hazard functions
- ❑ Number of simulated trials (up to 500)

Simulation Methods (Scenarios)

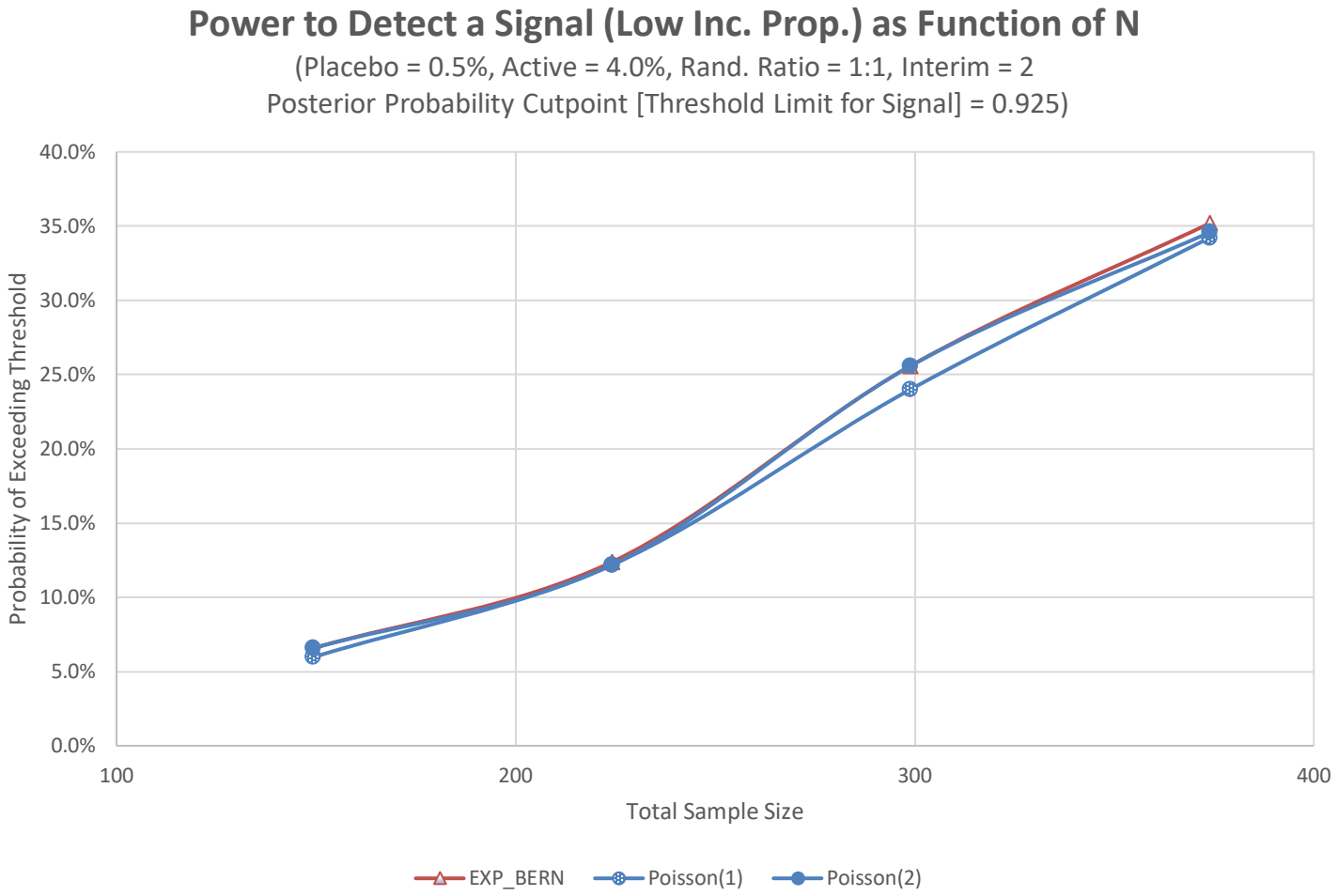
Hazard Ratio	Under-lying Dis-tribution	Sim-ulation No.	IR Scenario	Parameter	Pbo	Act (at Final Time-point)	Visit	Approx. Total N
Constant	Expo-nential	1.1 - 1.4	Low	Wk 52 IP	0.5%	4.0%	Interim 2	150 - 375
		2.1 - 2.4	Medium	Wk 52 IP	10%	10 - 25%	Interim 2	150
		3.1 - 3.4	High	Wk 52 IP	30%	30 - 50%	Final	200
De-creasing	Log-logistic	4.1 - 43	Low/ Medium	μ (inter)	9.85	9.85, 8.35, 7.4	Interim 3	375
				σ (scale)	2.0	2.0		
				Wk 104 IP	5.0%	5.0 - 15.1%		
		5.1 - 52	High	μ (inter)	6.17	6.17	Interim 1, 2, 3	200 - 400
				σ (scale)	1.6	1.6		
				Wk 52 IP	20.0%	20.0%		
In-creasing	Log-logistic	6.1 - 6.4	Low/ Medium	μ (inter)	7.3	7.3, 6.5, 6.1, 5.85	Interim 4	150
				σ (scale)	0.8	0.8		
				Wk 104 IP	3.5%	3.5 – 18.1%		
		7.1 - 7.4	High	μ (inter)	5.85	5.85, 5.5, 5.15, 5.07	Final	150
				σ (scale)	0.7	0.7, 0.7, 0.6, 0.7		
				Wk 104 IP	15.2%	15.2 – 35.3%		

Simulation Results (Constant Hazard Rates)

- Results (1.1 – 1.4)

Power Curve (by N)

No differences with low AE rates

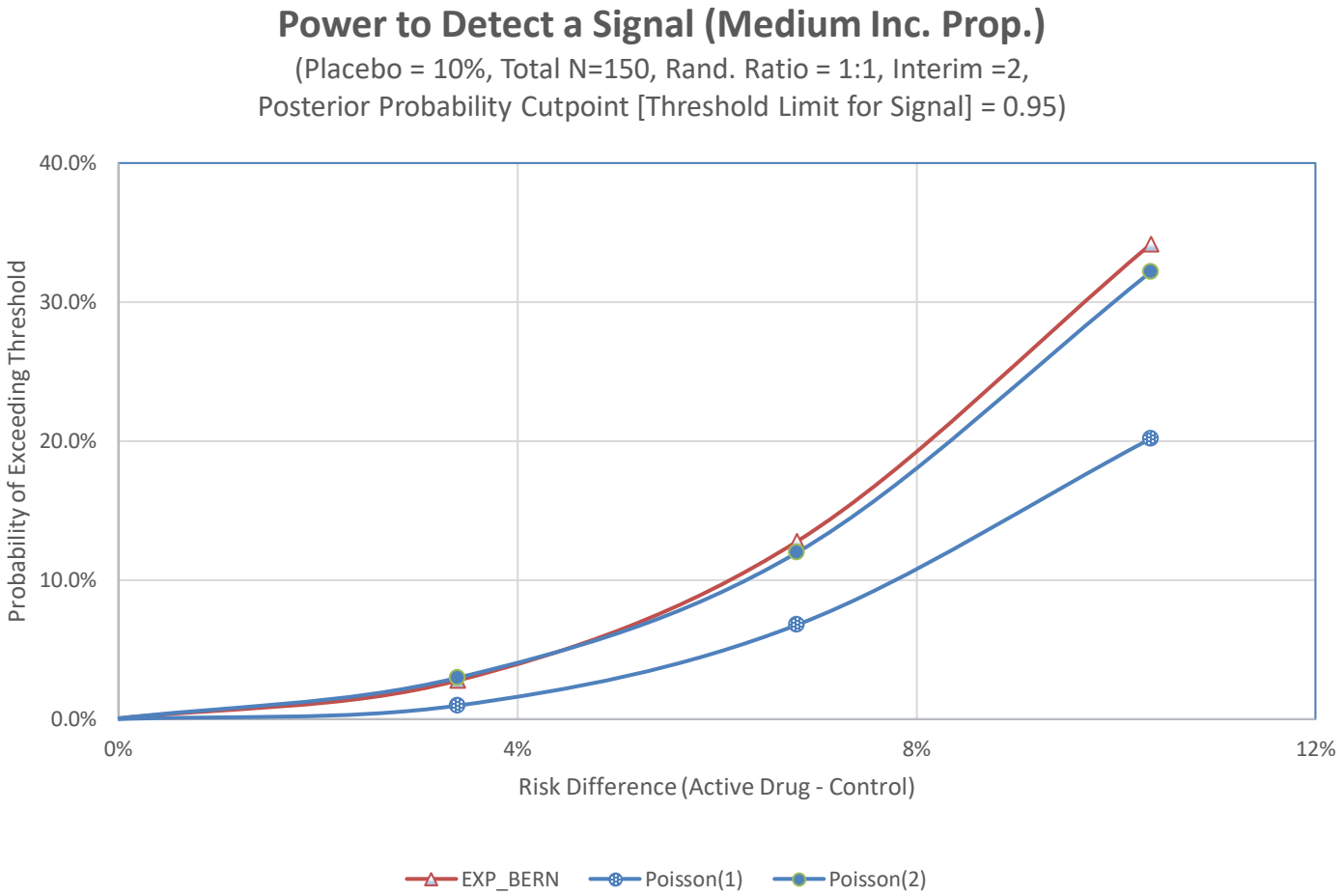


Simulation Results (Constant Hazard Rates)

- Results (2.1 – 2.4)

Power Curve (by RD)

Differences in Poisson models (with using total FU vs total Time-at-risk)



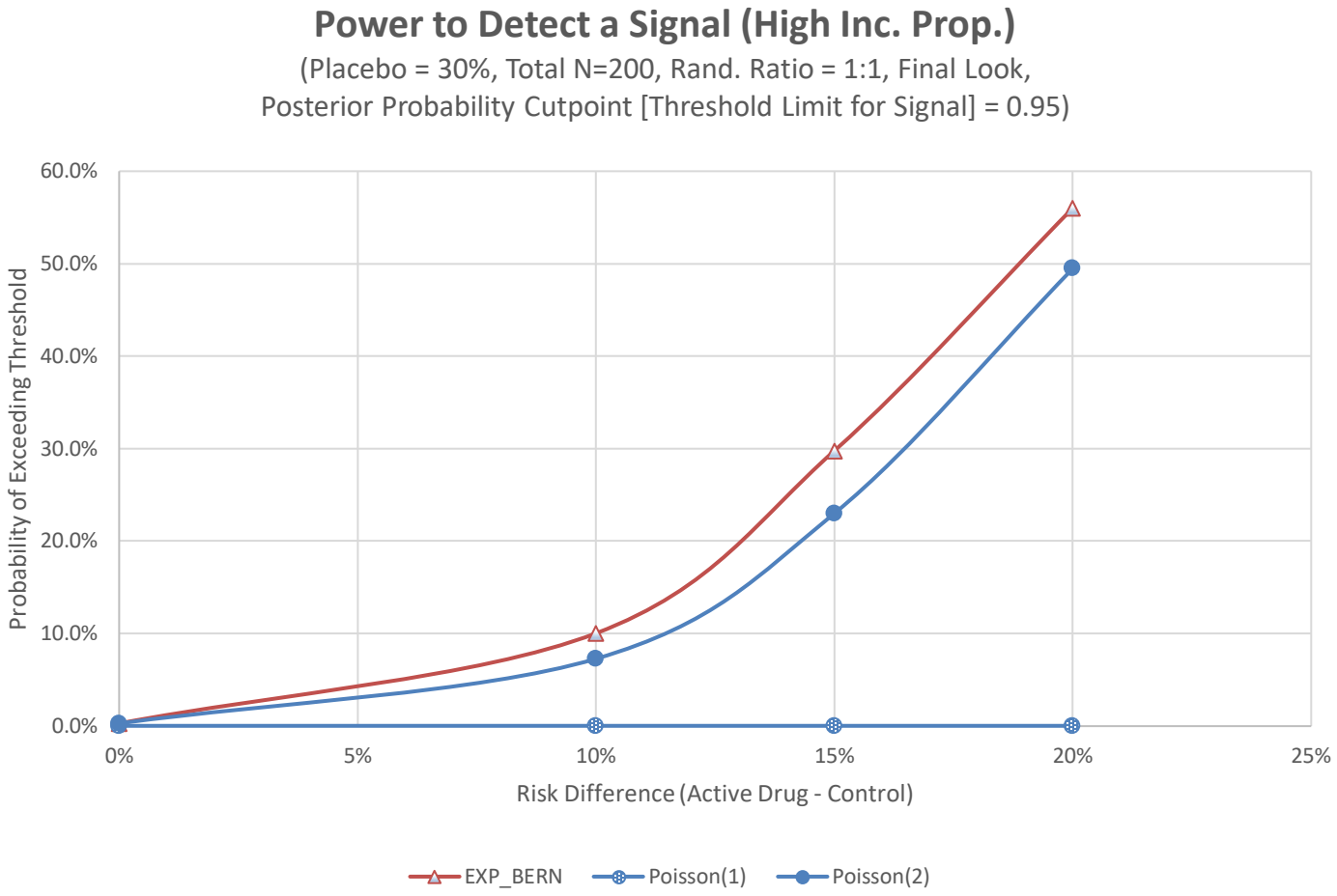
Simulation Results (Constant Hazard Rates)

- Results (3.1 – 3.4)

Power Curve (by RD)

Poisson(2) not viable

Improved Power with EXP_BERN

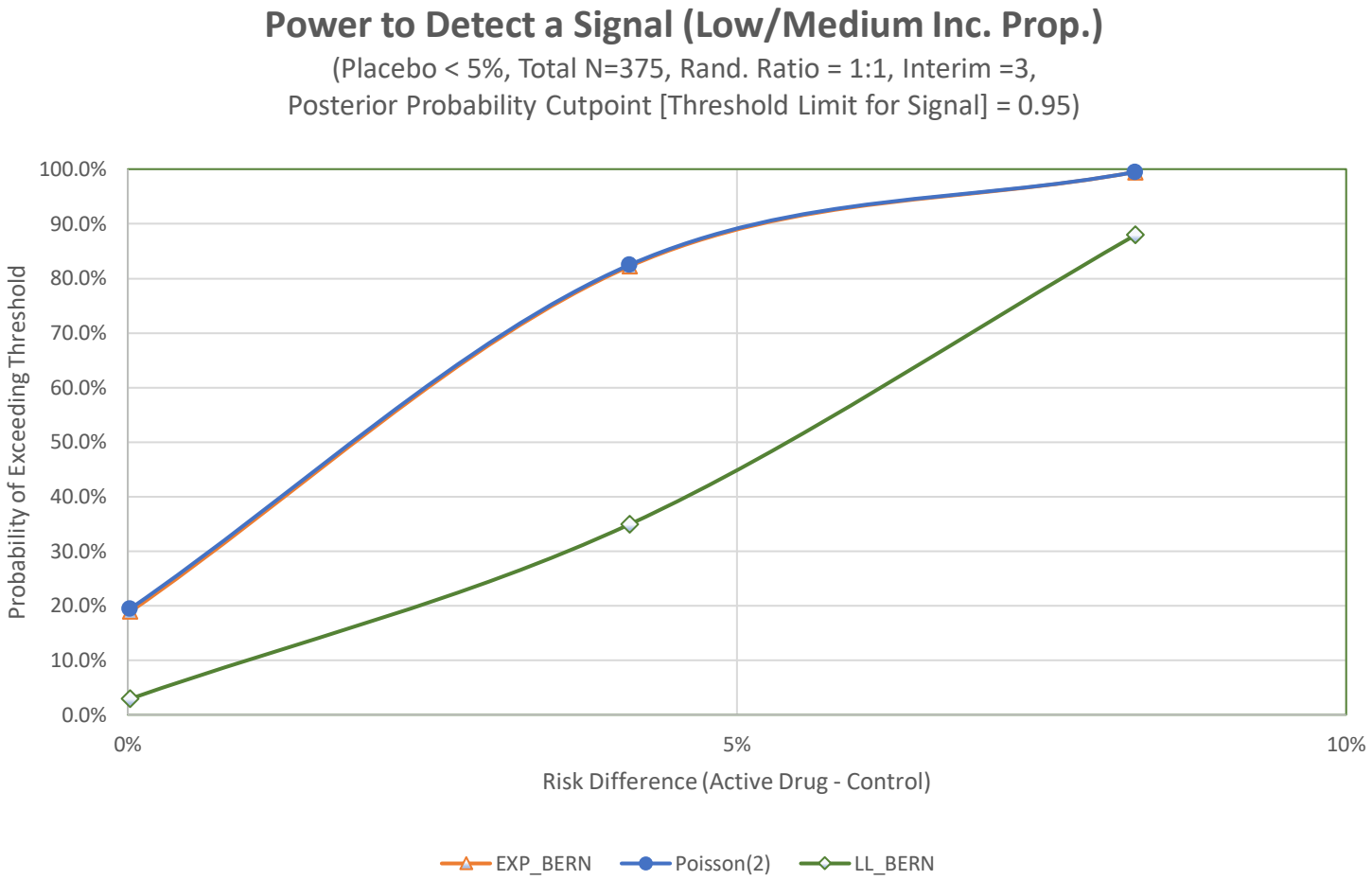


Simulation Results (Non-constant Hazard Rates - Decreasing)

- Results (4.1 – 4.3)

Power Curve (by RD)

Unacceptable false positive rates for Poisson and EXP_BERN models

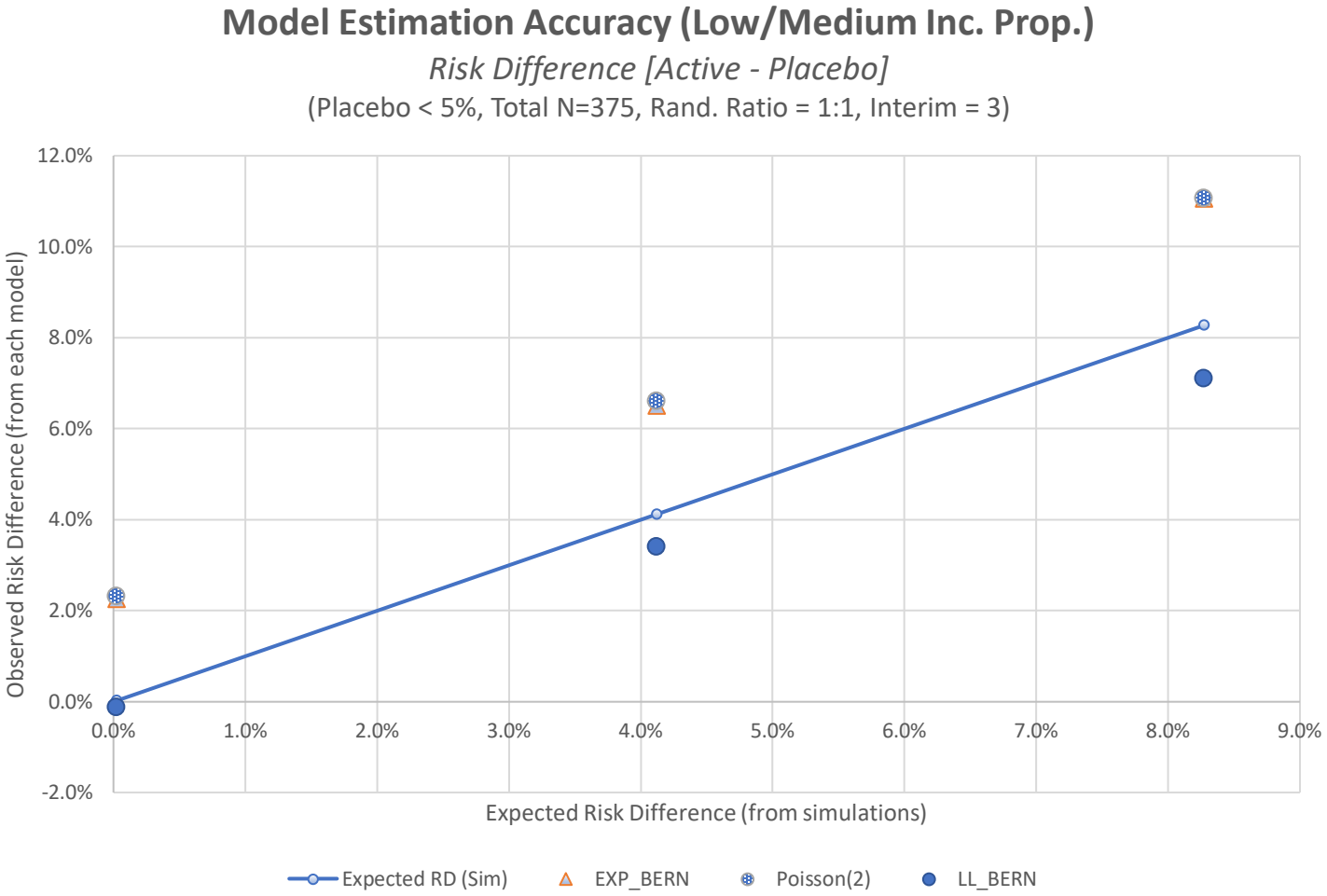


Simulation Results (Non-constant Hazard Rates - Decreasing)

- Results (4.1 – 4.3)

Model Estimation Accuracy

The LL_BERN model is much more precise than the other models (in which the RD is consistently over-estimated).

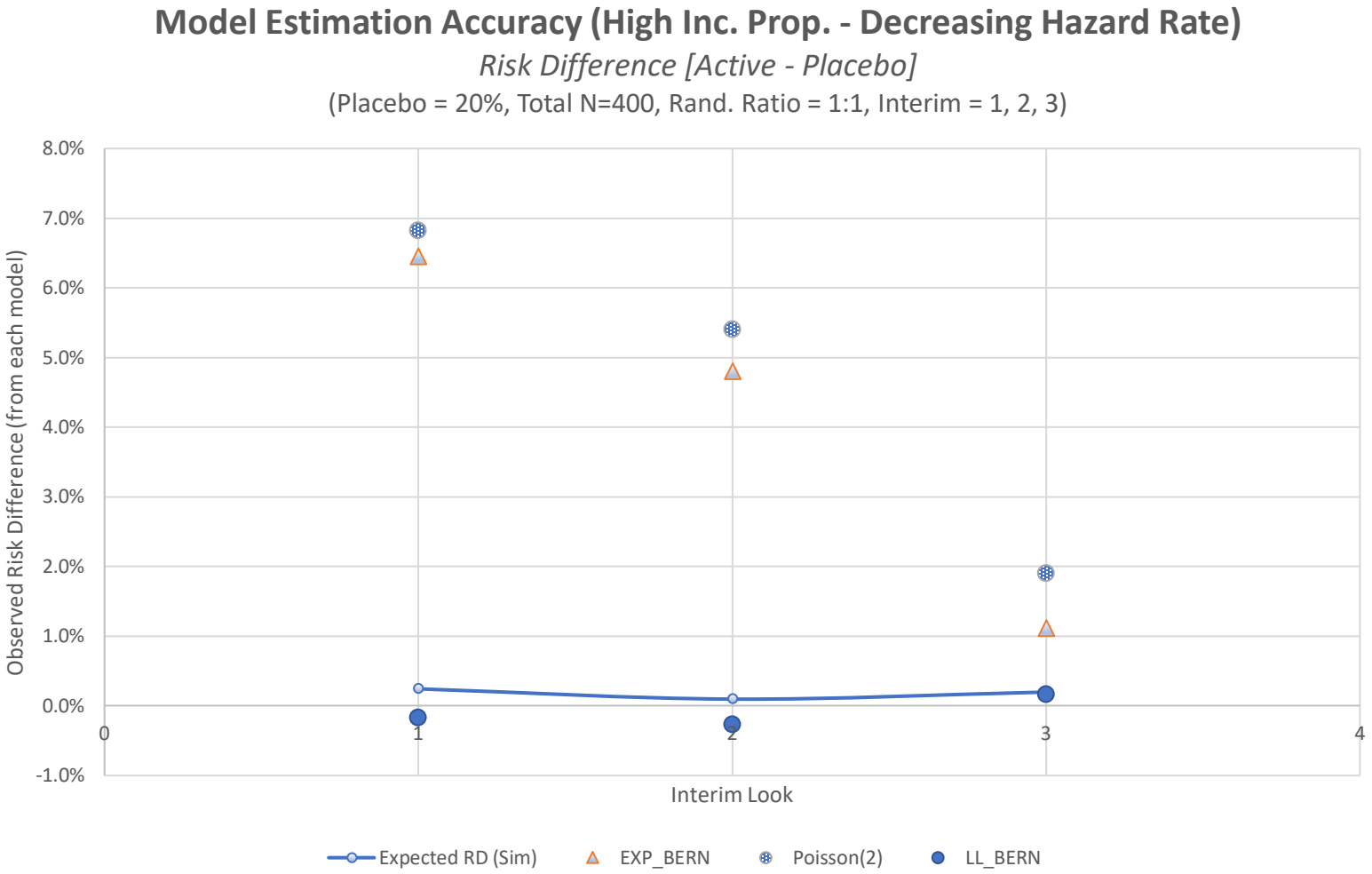


Simulation Results (Non-constant Hazard Rates - Decreasing)

➢ Results (5.1)

Model Est-imation Accuracy:

Substanial Errors from EXP_BERN and Poisson (2) Models – False Positive rates > 40%

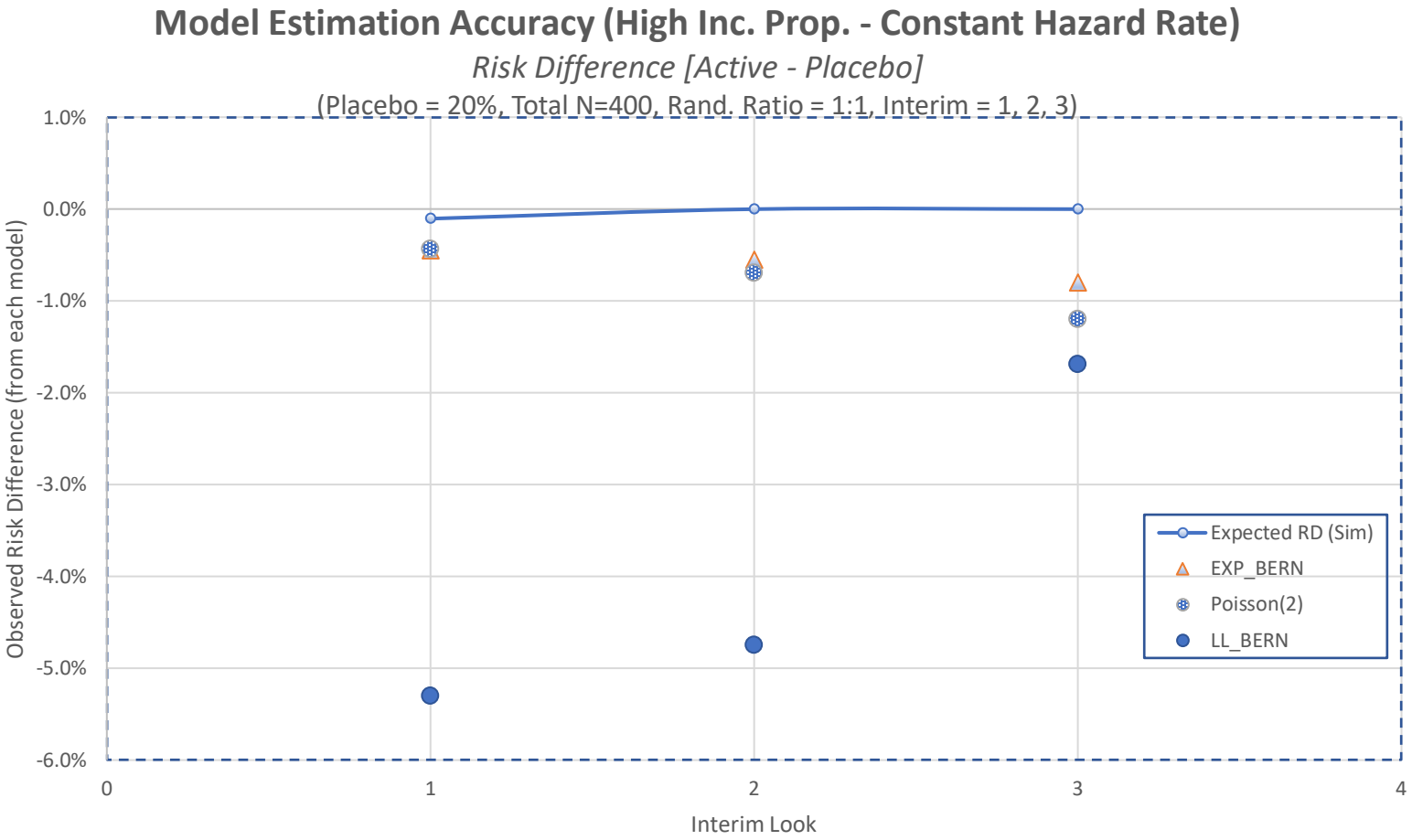


Simulation Results (Constant Hazard Rates -)

- Results (5.2)

Model Est-imation Accuracy:

Opposite pattern emerges compared to Result 5.1. Estimation error from LL_BERN Model.

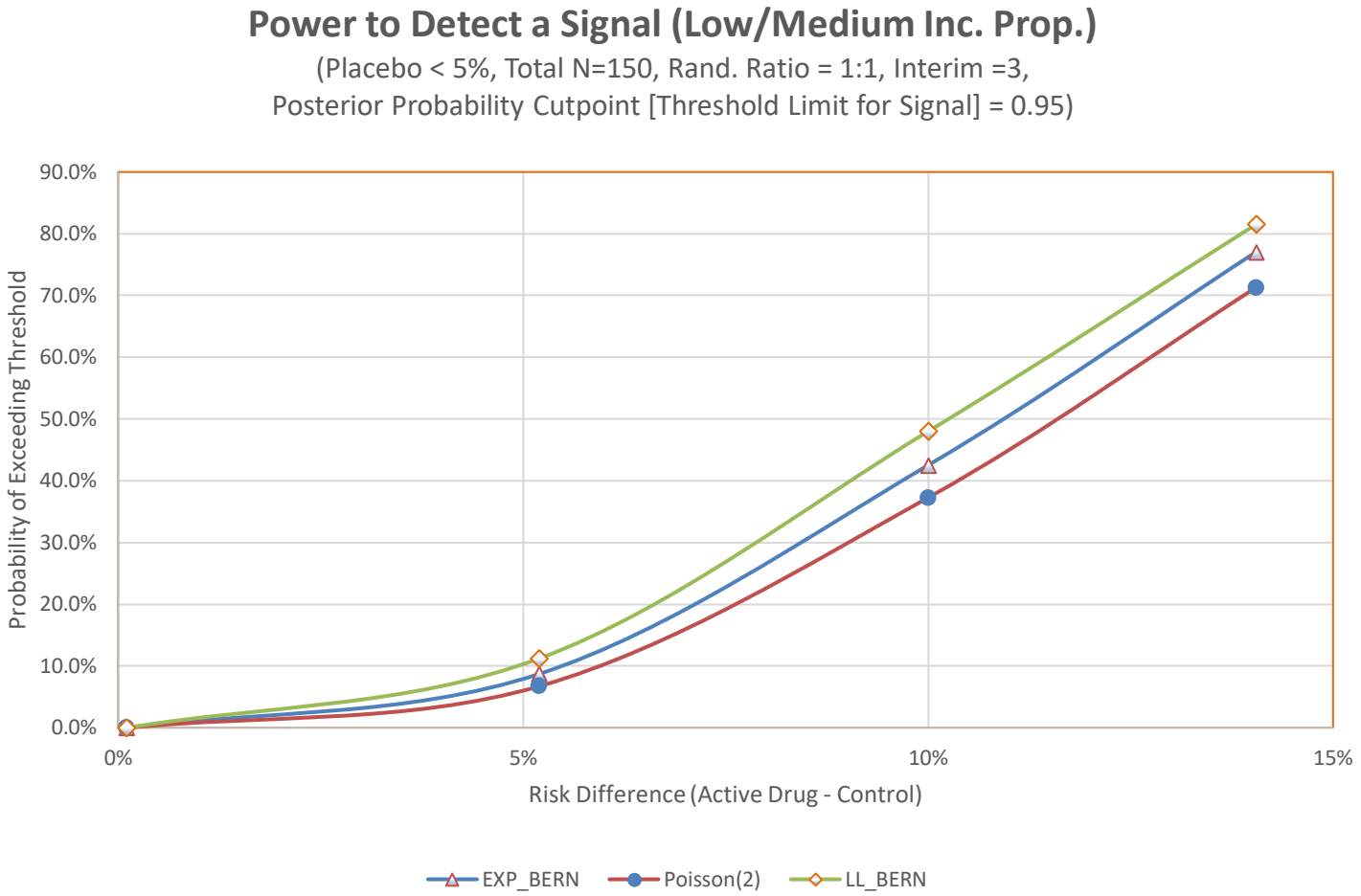


Simulation Results (Non-constant Hazard Rates - Increasing)

- Results (6.1 – 6.4)

Power Curve (by RD)

Improved Power with LL_BERN model

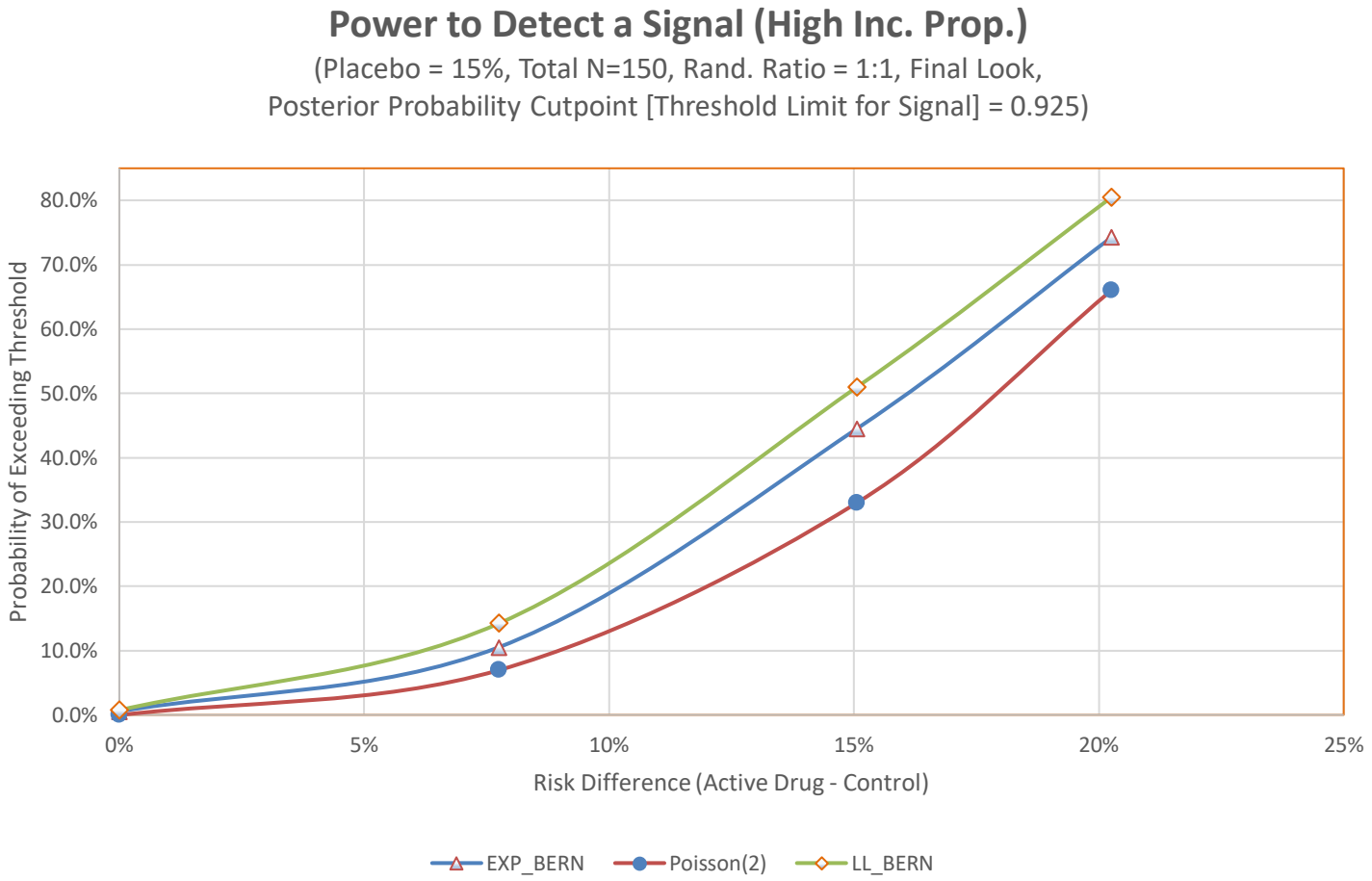


Simulation Results (Non-constant Hazard Rates - Increasing)

- Results (7.1 – 7.4)

Power Curve (by RD)

Noticeable drop in power for Poisson model



Simulation Results (Discussion / Summary)

Models assessed by event estimation accuracy, empirical power (sensitivity), false-positive rates (specificity)

- Constant Underlying Hazard Rates:
  - With low event rates (e.g., < 5% IP 1-year rate) all assessed models were comparable
  - With medium to high rates:
    - The Poisson (bdribs) model must be run using adjusted exposure time (excluding time after the event).
    - The EXP_BERN model performs reasonably well and gives slight improvements in accuracy and power (specificity).

- Non-constant Underlying Hazard Rates
  - With decreasing hazard rates (and larger sample size) the Poisson and EXP_BERN models produce inaccurate event estimation and unacceptable false-positive rates. The LL_BERN model performs much better.
  - With increasing hazard rates, the LL_BERN model produces better event estimation and superior power. The EXP_BERN model slightly out-performs the Poisson model (with adjusted exposure time).

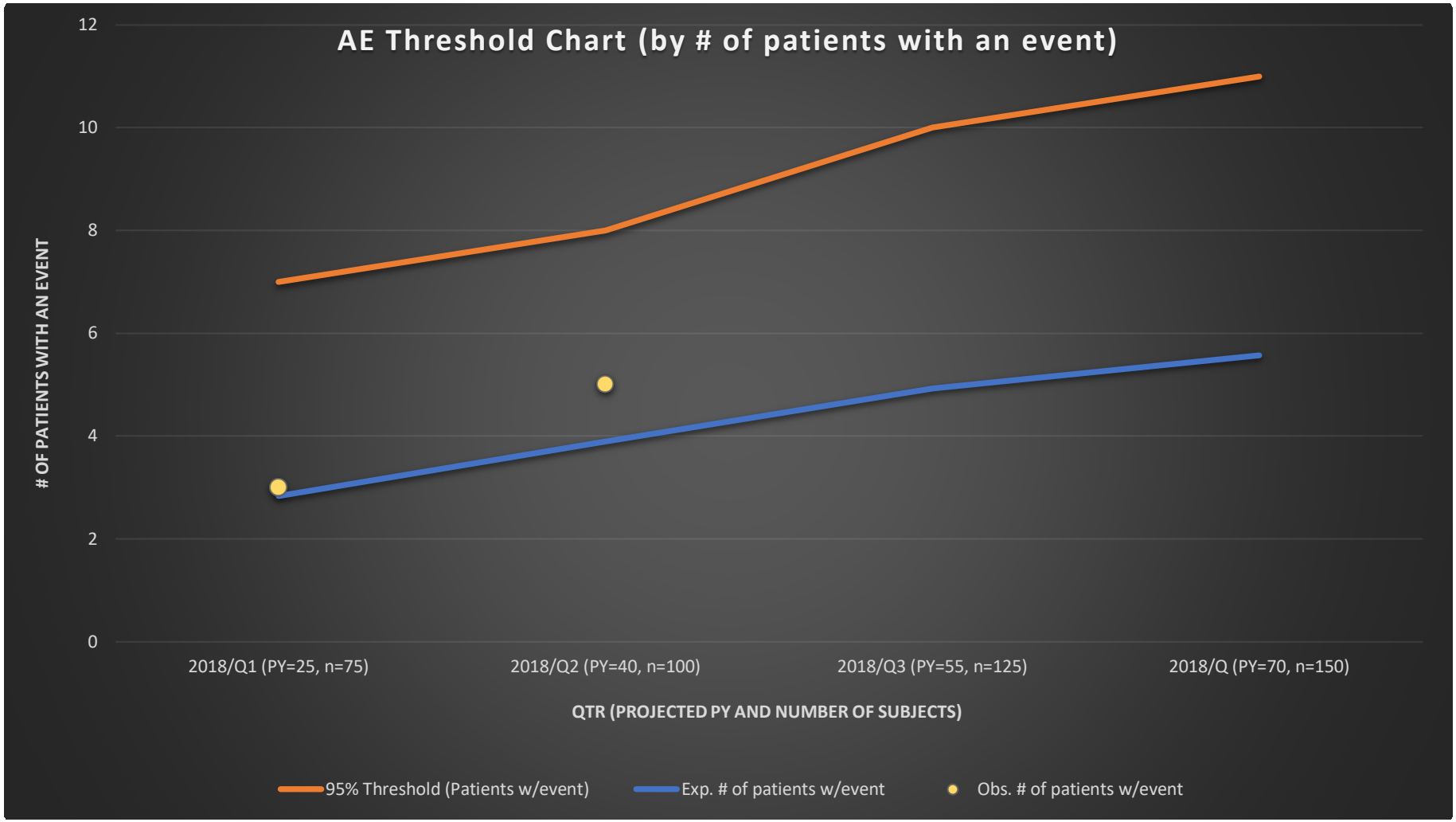
Simulation Results (Discussion / Summary)

Practical Considerations

- Poisson (bdribs) model runs much faster and is easily used to make projections with additional exposure patient-years (preferred method with small rates and constant hazard rates)
- With larger rates, the EXP_BERN model is a bit more sensitive in finding safety signals, but run-time is noticeably slower.
- With non-constant hazard rates, the LL_BERN provides a noticeable boost in sensitivity (power) without increasing false positive rates, but run run-time is also an issue.
- In real-world applications we don't always have a good handle on the characteristics of our data. The proposed models may serve as good sensitivity checks to the more standard Poisson-based models.
- Real-world applications in which Poisson models may not hold include SSD for malignancies (increasing hazards over time), survival studies (in which blinded monitoring is conducted initially), significant events in oncology studies (in which adverse event rates tend to be much higher).

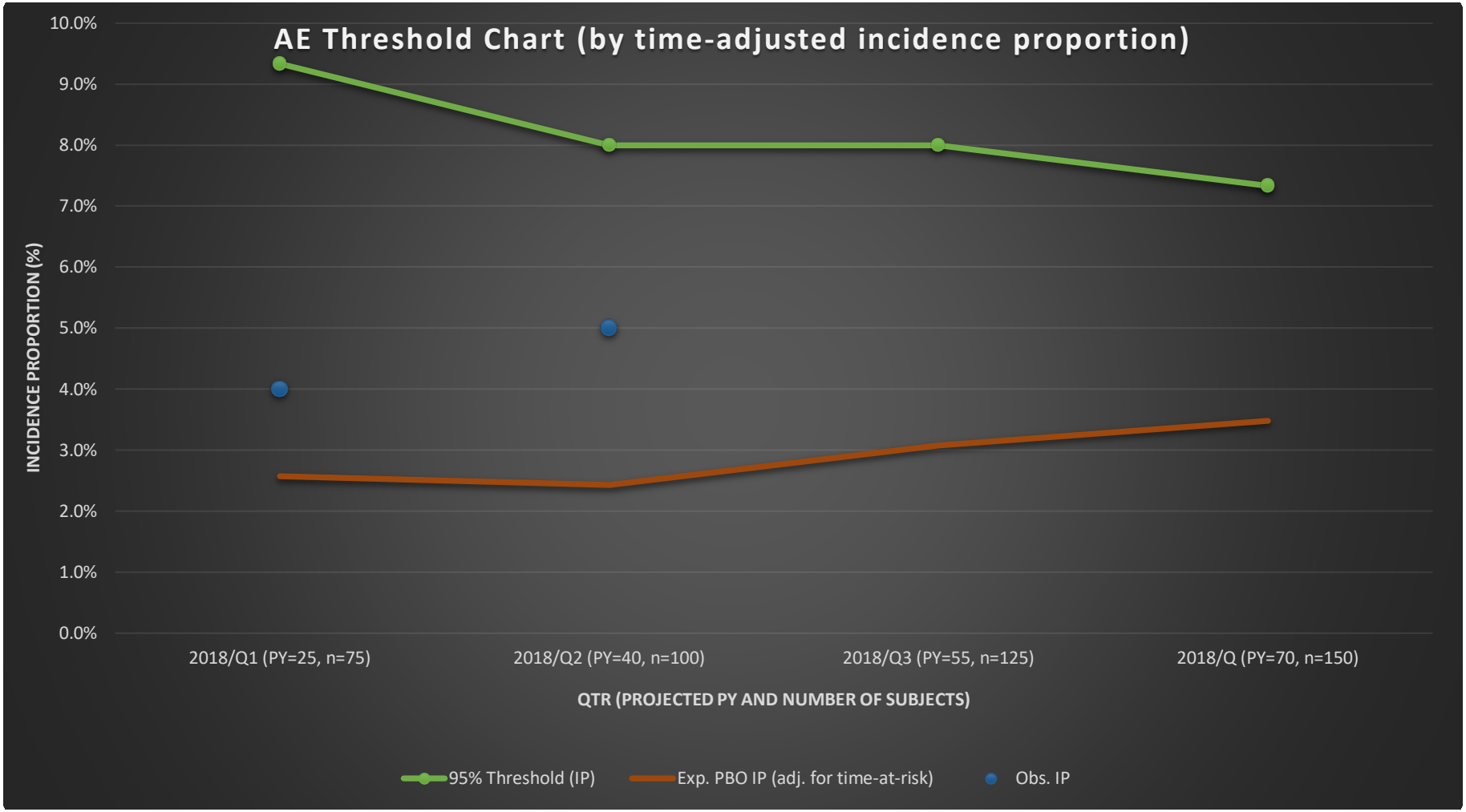
SSD Visualization: (Threshold Plots)

- Incidence (count): Alternative Look



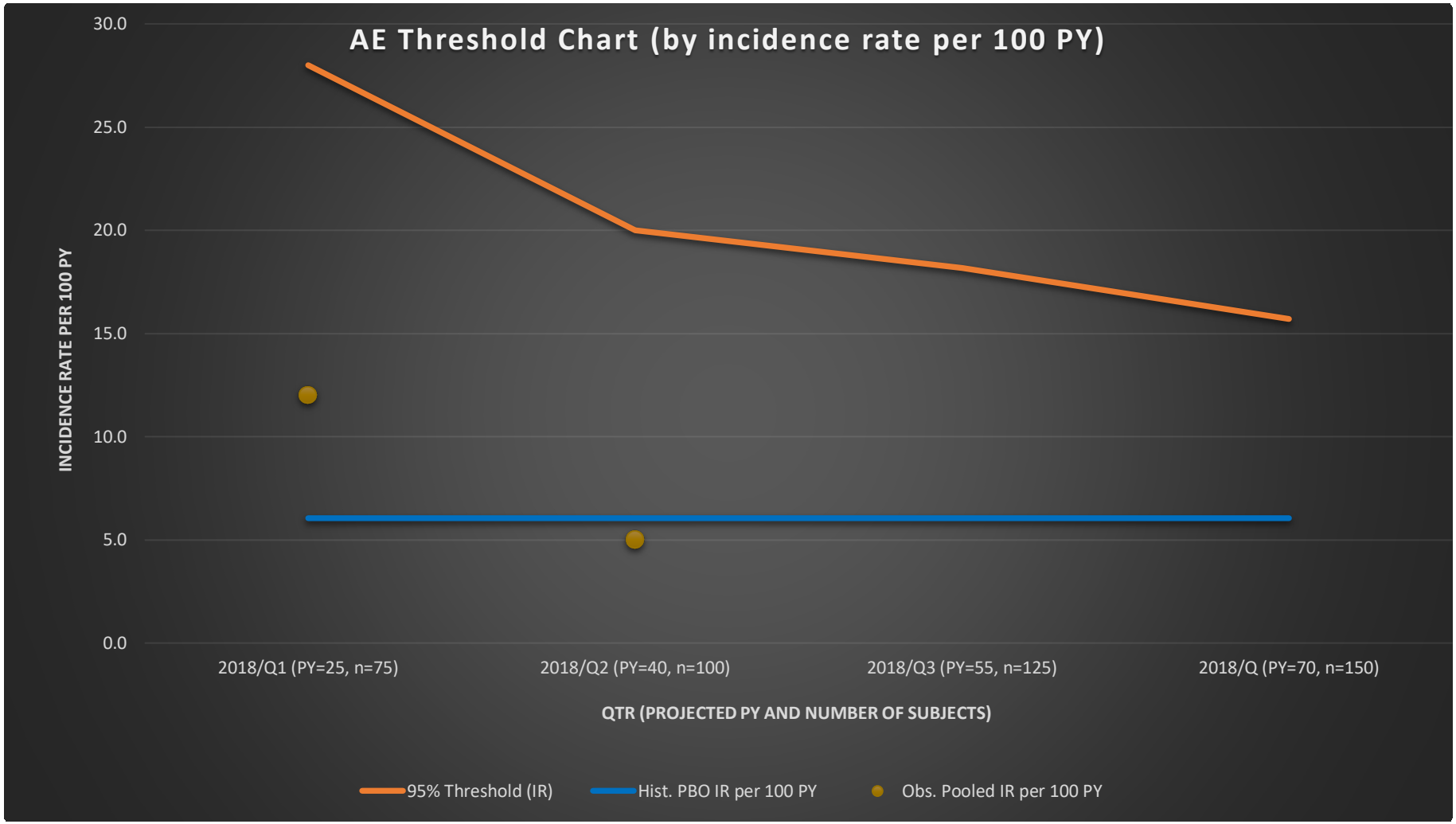
SSD Visualization: (Threshold Plots)

- Incidence Proportion



SSD Visualization: (Threshold Plots)

- Incidence Rate



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Lessons Learned / Final Thoughts / Conclusion

Additional Research

- Improved coding for faster program run-times so that operating characteristics of models can be done in a timely manner.

- Choice, selection and impact of priors on outcomes (note: Prior selection has a significant impact on outcomes).
  - Incorporate methods to estimate prior ESS (to ensure fair model comparison when developing models and investigating operation characteristics)

- Other models (time-to-event), exponential piece-wise, log-normal distributions, Weibull, negative-binomial, etc.

Expansion of SSD

- Expansion within and beyond AE Analysis

  - Incorporation of additional features to better control historical populations (e.g. Poisson regression, propensity scores, better methods/process for down-weighting historical data, etc.)
  - Multiplicity control (finding the proper balance)
  - Expansion to Vital signs, clinical labs, and ECG data
  - Visualization Tools and Dashboard Displays

Lessons learned / final thoughts / conclusions

- Final Thoughts / Summary

  - Continued development of SSD and all Standardized Safety Evaluation and Analysis is Critical
  - The Bayesian Framework provides a useful tool for conducting SSD analysis with continuous updating and aggregation of clinical trials data
  - Simulations provide a comprehensive method for evaluating methods and testing ideas
  - Understand underlying data distributions to select the appropriate model.
  - Expansion to other safety domains should be developed:
    - Clinically significant lab and ECG findings can be analyzed using a similar Bayesian framework

Questions?

Thanks

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