BORROWING EXTERNAL CONTROLS FOR AN EVENT-DRIVEN PEDIATRIC TRIAL IN PAH: A CASE STUDY

Adele Morganti, Matthieu Villeneuve Actelion JNJ Biostatistics
Cristina Sotto, An Vandebosch JNJ SDS-SMM

OUTLINE

- Pediatric PAH - Background
- Case study: borrowing external controls for an event-driven pediatric trial in PAH
- Conclusions

PEDIATRIC PAH – BACKGROUND

Rare disease affecting the vessels of pulmonary circulation

- Adult efficacy proven by time to disease progression or exercise capacity.

Partial extrapolation accepted by HAs

- **No PD/intermediate endpoint** that can be defined across pediatric subsets
  - > Effect on pulmonary vascular resistance requires invasive approach, unacceptable in children (nowadays)
  - > Exercise capacity can only be assessed in developmentally able children

PEDIATRIC PAH – BACKGROUND (CONT)

As of today, **time to disease worsening** represents the only clinically meaningful efficacy endpoint to study PAH in the pediatric patients (Gomberg-Maitland 2013)

Conducting event driven study is challenging due to:

- the rarity of the disease
- increasing off-label use in the pediatric patients

STANDARD SUPERIORITY EVENT-DRIVEN DESIGN

Standard TTE Design

- accrual rate=5/months
- max study duration=60 months
- 50% survival @18 mos. for CONTROL
- HR=0.6 (from adult study)
- 1-sided significance level=2.5%
- 1:1 randomization

➢ **N=205**

- power >80%
- **events: 129**

TTE=time to event; HR=hazard ratio;

Based on HA interactions:
Strict control of type I at 0.025 (1-sided)

Sponsor concern:
Power > 80% (linked to conclusiveness for FDA discussion for written request)

Study duration needs to meet regulatory timelines

A POSSIBLE SOLUTION: BORROWING CONTROLS

Decrease sample size by borrowing **external controls** from an ongoing pediatric PAH trial with a different drug and same primary endpoint

Fit with Pocock criteria (1976) external control

1. same SoC treatments
2. contemporary with same eligibility criteria
3. same endpoint: time to disease progression(with adjudication)
4. WHO group 1, same etiology
5. similar geographical landscape
6. patient selection and accrual expected to be similar

<u>Only one</u> contemporary data source for external controls!

ROBUST PRIOR

- Bayesian methods for incorporating external control information for a new trial → **exchangeability** assumption
  - always a possibility of *prior-data conflict*

- Robust approach
  - combines an informative and a vague prior, appropriately weighted

$$\underbrace{p(\theta)}_{\text{mixture prior}} = \underbrace{w_1\, p_1(\theta)}_{\text{informative part (precise information from external data)}} + \underbrace{(1-w_1)\, p_2(\theta)}_{\text{vague part}}$$

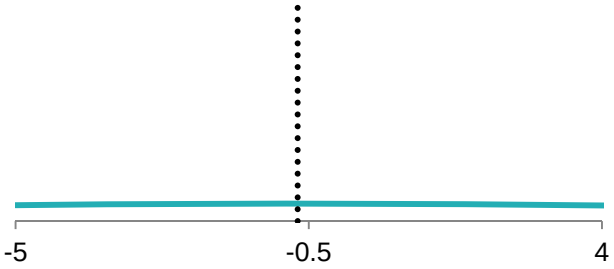
  - updated (posterior) weights shift to the corresponding component depending on the degree of *(dis)similarity*

Schmidli *et al*. (2014) *Biometrics* **70**: 1023-1032.

BAYESIAN INFORMATIVE PRIOR

PRIOR for
log(HR) =
$\log(\lambda_a) - \log(\lambda_c)$

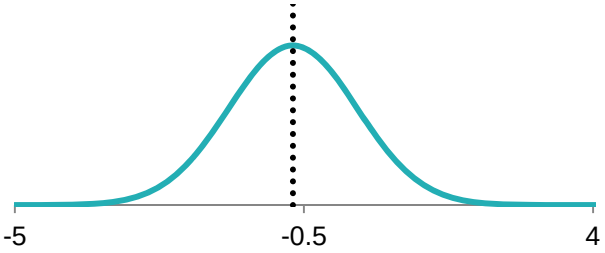
ACTIVE



$\log(\lambda_a)$

VAGUE

CONTROL



$\log(\lambda_c)$

INFORMATIVE

Asymptotic Normal distribution approximation of log (HR) is used

We applied **robust prior and power prior** approaches for $\log(\lambda_c)$ and compared the operating characteristics in this context.

PAH EVENT-DRIVEN TRIAL: BAYESIAN APPROACH

Simulations were performed to explore operational characteristics

PRIOR :

ONGOING TRIAL FOR CONTROL

Robust Prior Approach

- weight of informative part: 0.7, 0.9
- vague/informative variance ratio:1000
- no. of events for CONTROL in parallel trial: 20, 40
- 10,000 simulated trials
- varying control event rate

Power Prior Approach

- full borrowing (alpha=1)
- static

ACCUMULATED DATA:

TRIAL ON NEW DRUG VS. CONTROL

Standard TTE Design

- accrual rate=5/mo.
- 50% survival @18 mos. for CONTROL
- HR=0.6 (from GRIPHON adult study)
- 1-sided significance level=2.5%
- 1:1 randomization

Sample size/events reduced to N=150 / 89

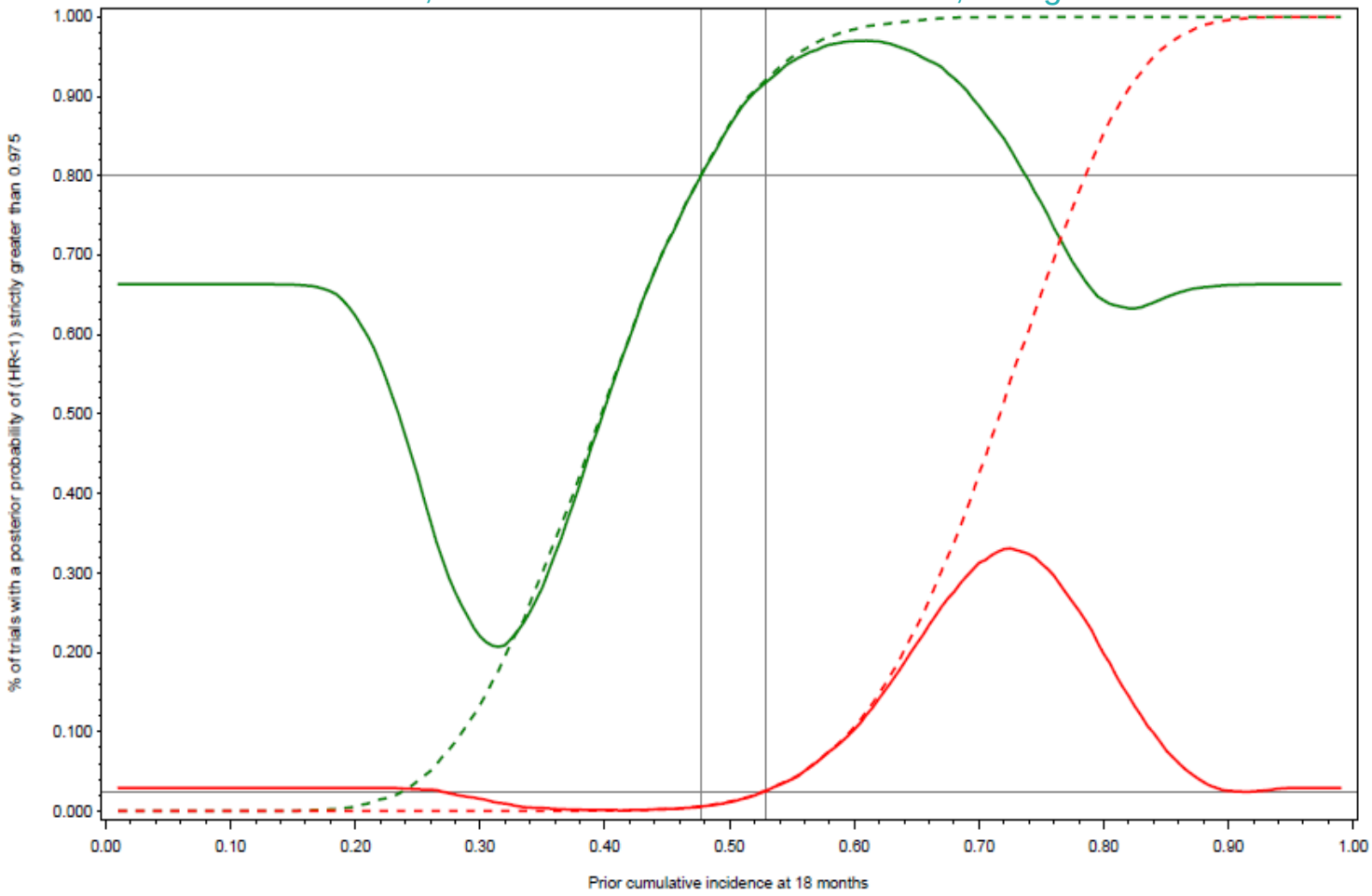
BORROWING WINDOW

Simulations were performed to identify an efficient borrowing window:

An efficient borrowing window was defined as:

- type I < 0.025 (1-sided)
- power >80%

Operational Characteristics: Type I Error and Power Varying the Event Rate of the External Control Group
40 Events Borrowed ; Accumulated Data: N=150 /e=89 ; Weight of informative Prior: 0.7



HR=0.60

robust prior

power prior

HR=1

robust prior

power prior

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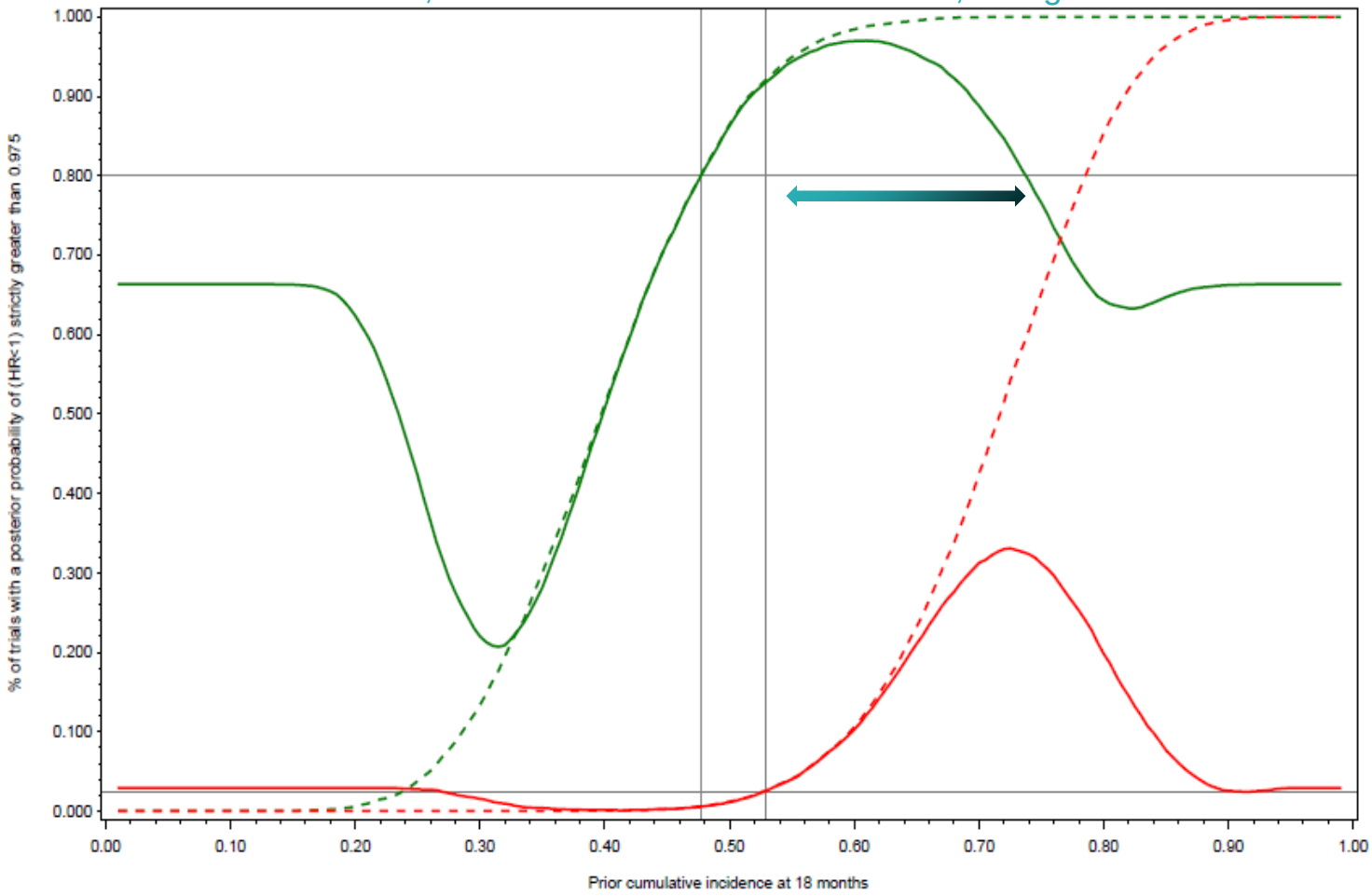

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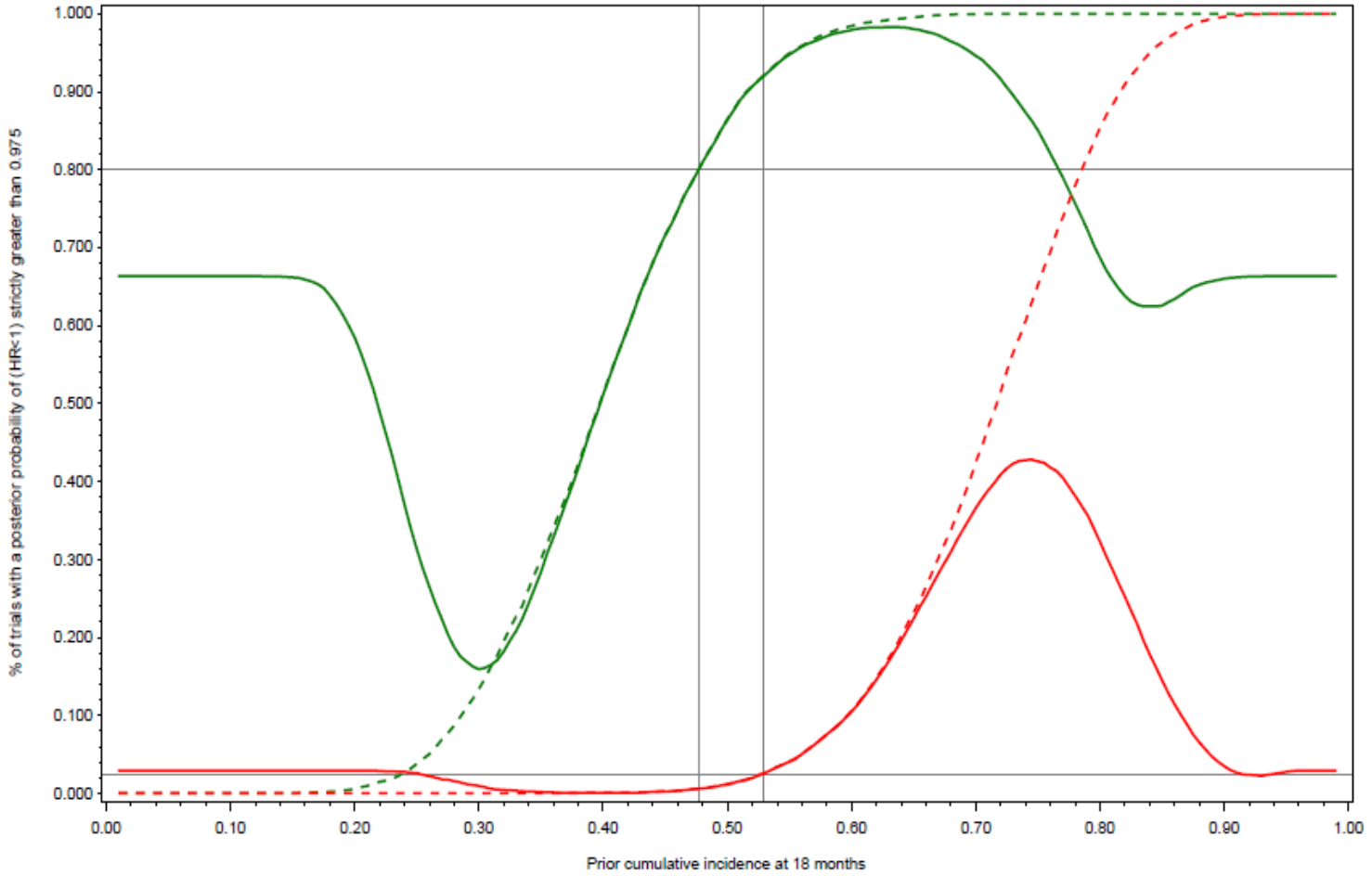

HR=0.60
- robust prior
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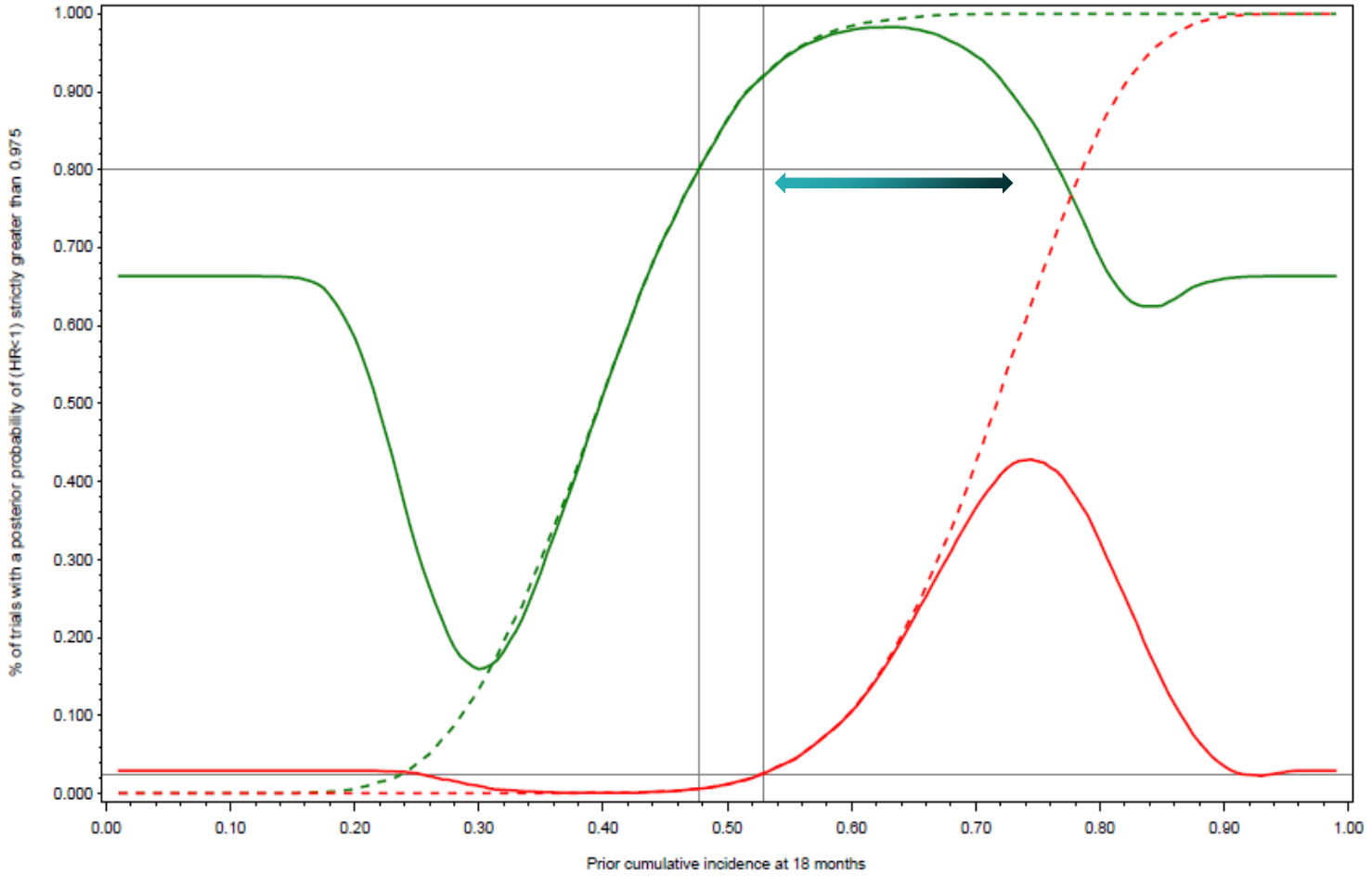

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- power prior

HR=1
- robust prior
- power prior

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CONCLUSIONS

- When strict type I and II error control is required, robust and power prior approaches require strict homogeneity between internal and external controls (low probability of success)

- The borrowing window is similar when comparing robust prior and power prior approach
  - varying the prior weight does not address departure from homogeneity in our case (only one source)

THANK YOU.

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BACK-UP

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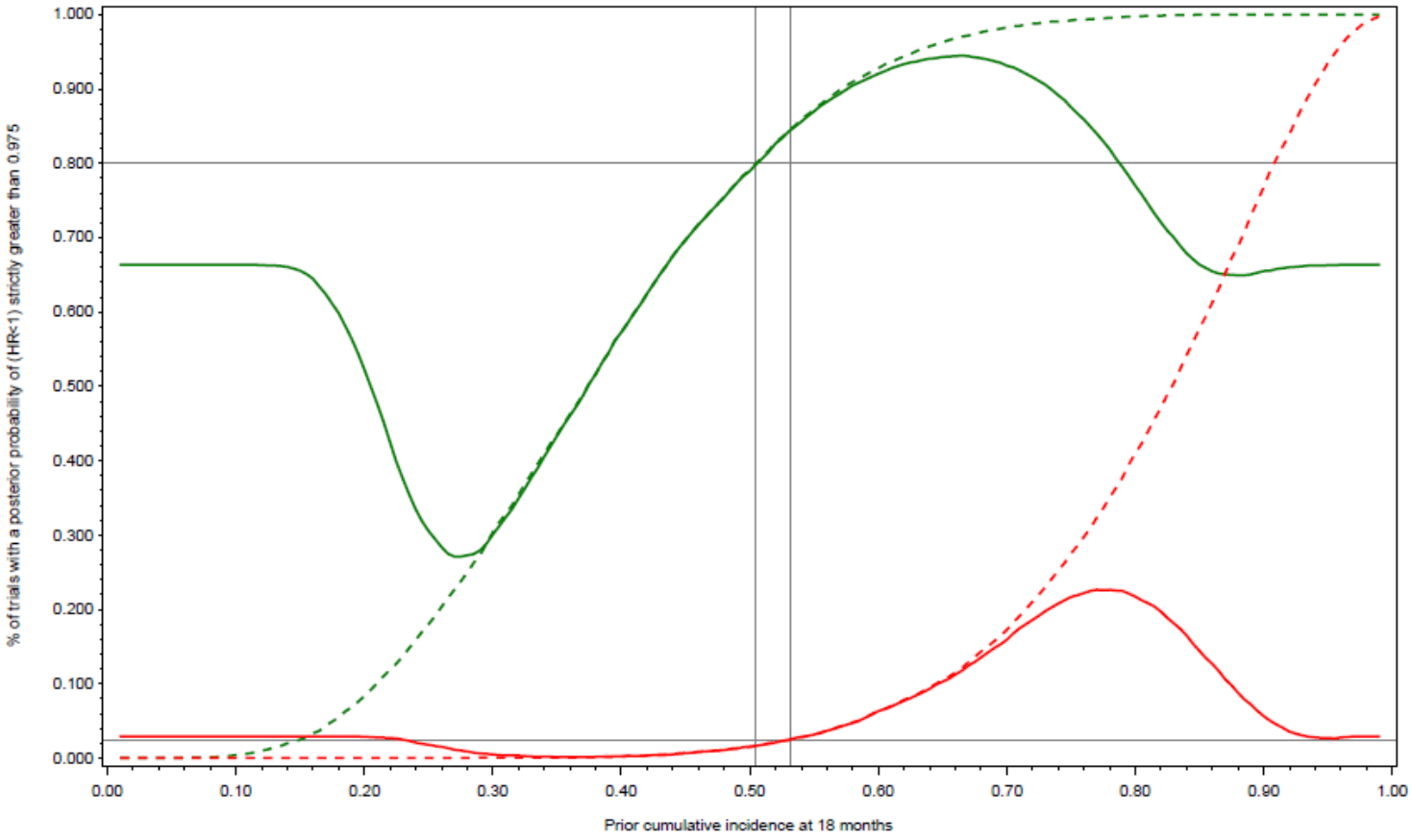

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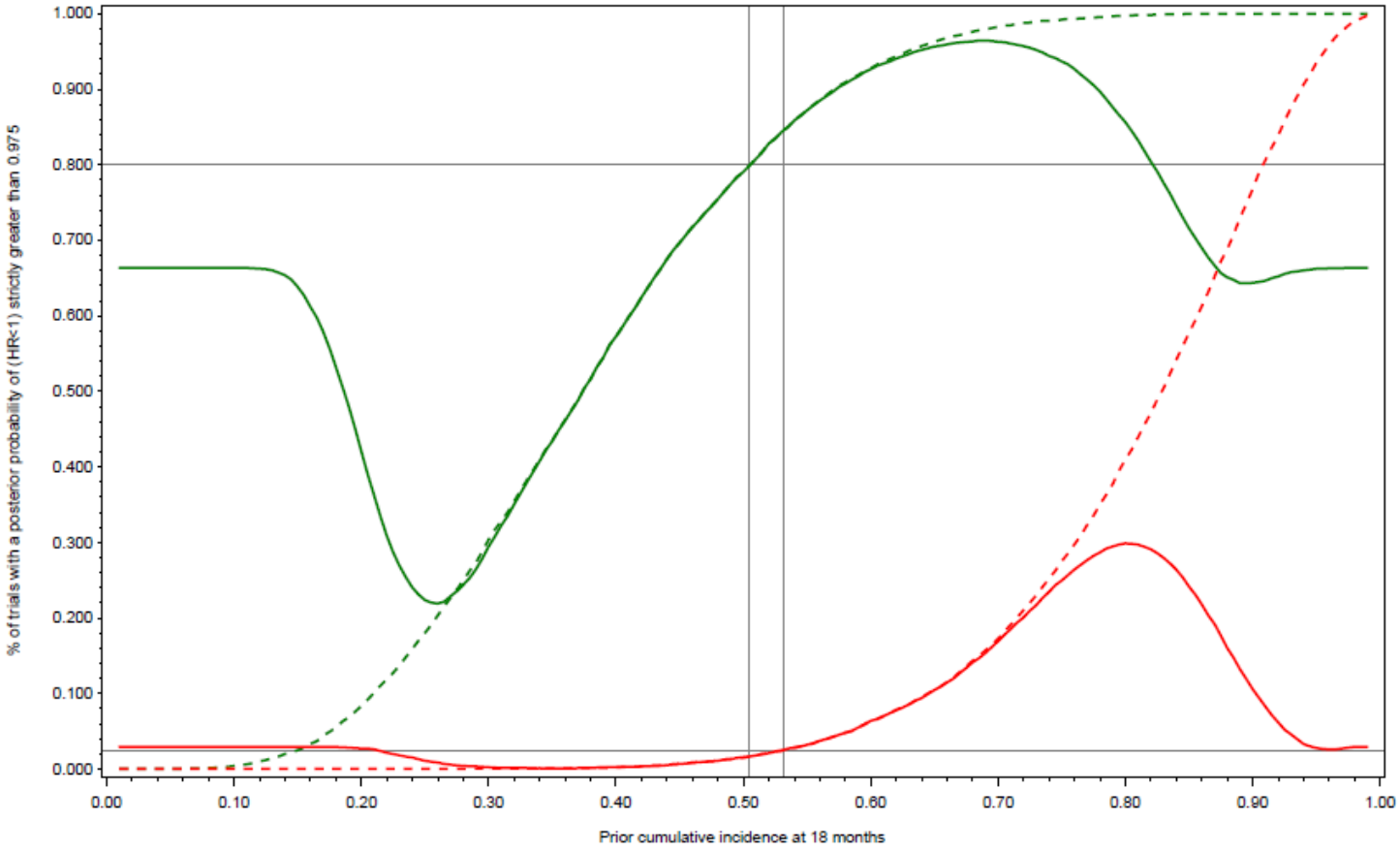

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