An Interim Monitoring Approach for a Small Sample Size Incidence Density Problem

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Statistical Setting

- Proposed research with an incidence density as the outcome of interest.
  - Can HIV+ patients with a history of cryptococcal meningitis be safely removed from their prophylactic doses of fluconazole?
- Denote the number of cases as X, and the observed person-time at risk as T. Then, the incidence density is defined as

$$ID = \frac{X}{T}$$

- X is assumed to follow a Poisson distribution.

Study Planning: Fixed Sample Power Analysis

- Null Hypothesis: ID = 0.05
- Alternative Hypothesis: ID = 0.02
- Significance Level: $\alpha = 0.05$
- Desired Power: $1- \beta = 0.80$

- Required Person-Time: T = 200 years.
  - Projected recruitment $\Rightarrow$ 3 years to complete study.

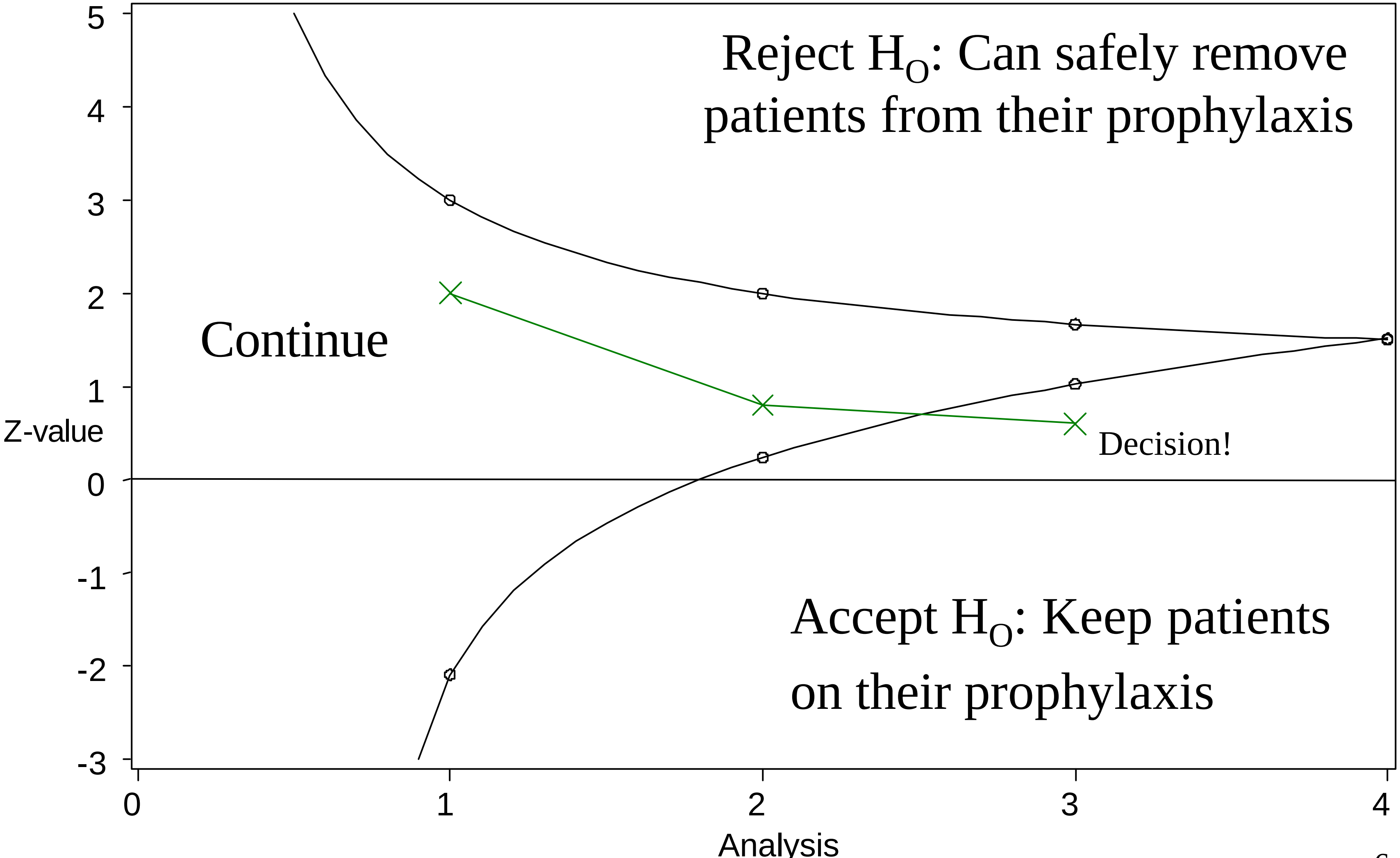
Practical Concern

- The outcome of interest often leads to death.
- Clearly, frequent interim monitoring will need to be conducted.
- Concern exists that a DSMB might be hyper-sensitive to early events.
- Want a statistical framework for making decisions regarding study continuation/termination.
  - Prevent unwarranted early termination of the study.
  - Allow early study stoppage for lack of safety.
  - Allow early study stoppage for efficacy.

Group Sequential Methods

- Allow for interim monitoring of data while achieving both an overall target Type I error probability and power.
- Yield sequences of critical values to be used in making decisions at interim stages of analysis.
  - Stop to reject null.
  - Stop to *accept* null.
  - Continue collecting data.
- Critical values depend upon each of the following.
  - Type I error rate, α.
  - The specified effect size, δ.
  - Desired power, 1- β.
  - Information, I.

An Illustration



Whitehead's Method

- Handles the case in which interim analyses are conducted at unequal increments of accumulated information.
  - Important because of the continuous and likely variable recruitment.
- Whitehead's method (as well as all other interim monitoring methods) assumes that the sequence of test statistics $S_1,\ldots,S_K$ follow a multivariate normal distribution.
- Can we make a case for a normal approximation to the Poisson in this particular setting? Well, eventually…

It Becomes Normal When?!?

- At the conclusion of the study (using the fixed sample approach described previously) we would have a Poisson mean of ~8 under the null. Standard texts deems this to be marginally adequate to support a normal approximation to the Poisson.
- Consequently, we cannot blithely conduct interim analyses via Whitehead's method by performing a normal approximation to the Poisson at each interim stage.

A Proposed Adaptation To Whitehead's Method

- Instead of working with the Whitehead boundaries directly, work with their associated p-values.
  - E.g., Interpret a Z-value of 1.96 as a p-value of 0.025.
- Compute exact Poisson p-values for the observed data.
- Compare the exact p-values to the Whitehead-based p-values. Accept, reject, or continue under the same logic as before.

Simulation Study: Parameter Ranges

- Alpha: 0.05
- Power: 0.80
- ID: 0.05 (null), 0.02 (alt), 0.005 (extreme)
- Recruitment Rates: 30, 40, 50, 70 per year plus an initial bolus of 40 subjects

Simulation Study: Data Generation

- For each of the 12 scenarios:
  - Determined the expected number of cases, E.
  - Sampled repeatedly from a Poisson(E) distribution to determine the number of events for each replicate.
  - Randomly placed each cases across the distribution of accumulated person-time.

Simulation Study: Interim Analyses

- Performed computations at regular time intervals.
  - Determined Whitehead boundaries.
  - Transformed boundaries into p-values.
  - Computed exact Poisson p-values for the simulated data.
  - Made decisions regarding study continuation/termination.

Results

Target Alpha / Power			0.05 / 0.80		
Simulated ID			0.05	0.02	0.005
Rec Rate	30	Alpha	0.038	-	-
		Power	-	0.758	1.000
		Mean Duration	32.2	34.3	25.1
	40	Alpha	0.031	-	-
		Power	-	0.834	1.000
		Mean Duration	29.9	33.9	25.2
	50	Alpha	0.026	-	-
		Power	-	0.871	1.000
		Mean Duration	28.2	32.1	24.4
	70	Alpha	0.045	-	-
		Power	-	0.923	1.000
		Mean Duration	26.3	28.0	24.0

* Maximum Duration: 42 months.

Discussion

- Why was the observed Type I error rate consistently less than 0.05?
  - Poisson p-values don't flow smoothly across 0.05, they leap over it.
    - E.g., if X~Poisson(4), then Pr(X=0)=0.018 and Pr(X=1)=0.092.
- Why was the observed power higher than the target level?
  - Time-based analyses resulted in overshooting the amount of information required to bring the boundaries together, thus increasing the power of our analysis.

Discussion

- Should we use this approach in the proposed study?
  - Mean duration always shorter - up to 12 months.
    - Maximum duration is 6 months longer.
  - Type I error rate controlled.
    - Precise Type I error rate not extremely predictable.
  - Desired power achieved.
  - True distribution of the data taken into account.
  - Allow for early stoppage (for safety or efficacy).

Conclusion

- The proposed method of interim monitoring would be most beneficial in the conduct of this study.

Study Population

- HIV positive patients
  - Compromised immune systems
- History of cryptococcal meningitis
  - Fungal infection
  - Potentially fatal
- Receiving prophylaxis
  - Fluconazole, an antifungal

Medical Facts

- Long-term fluconazole use is undesirable
  - Substantial cost
  - Side effects
  - Resistance development likely
    - Reduces treatment options for other fungal infections
- Advanced HIV drug therapy now exists
  - Patient immune systems being reconstituted
    - As measured by CD-4 counts

Study Question (in lay terms)

- Can we safely remove these ‘immune-restored’ patients them from their prophylactic fluconazole regimens?
  - I.e., are their immune systems sufficiently recovered to provide them with adequate protection from cryptococcal meningitis?

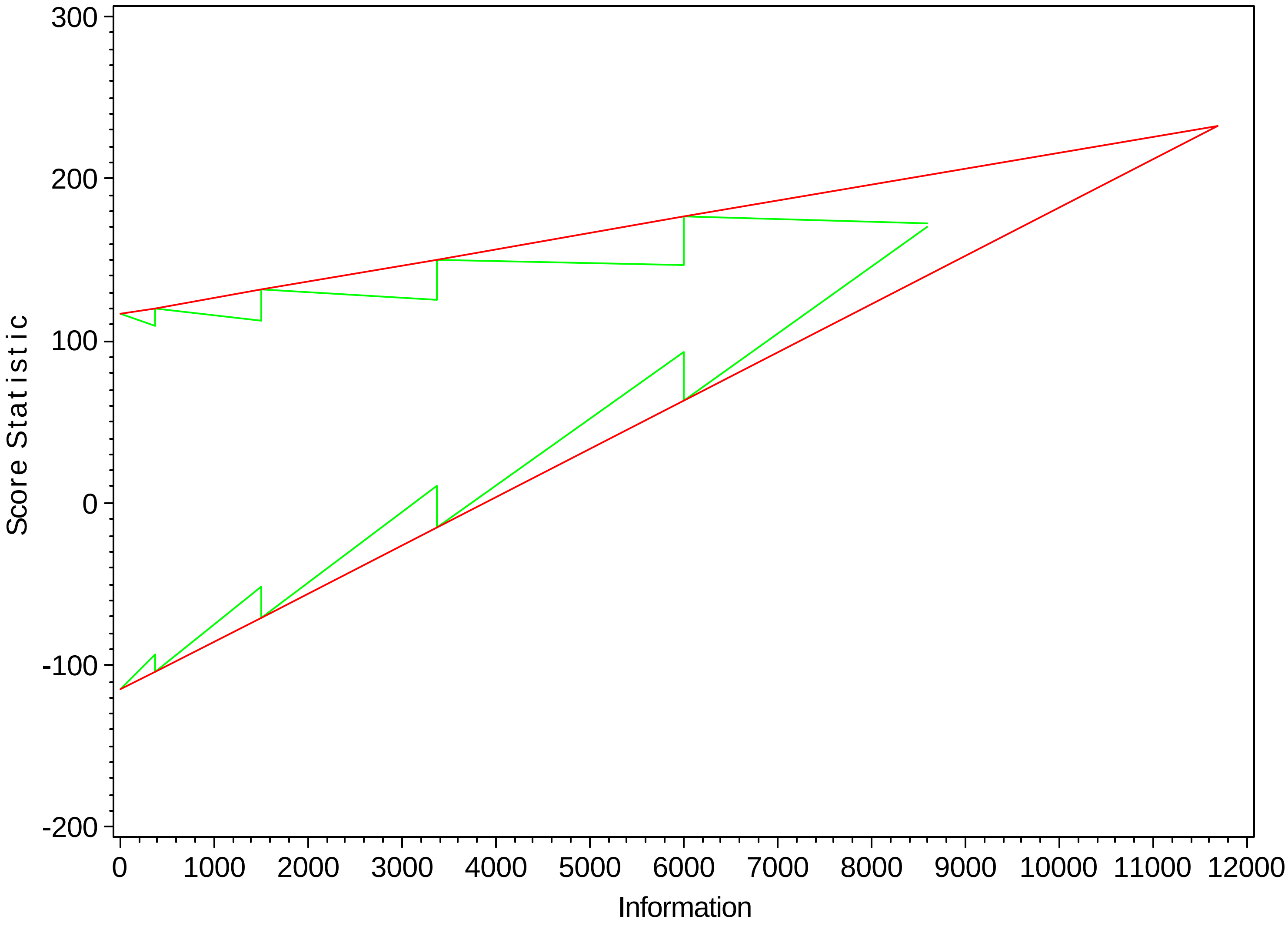
Study Design

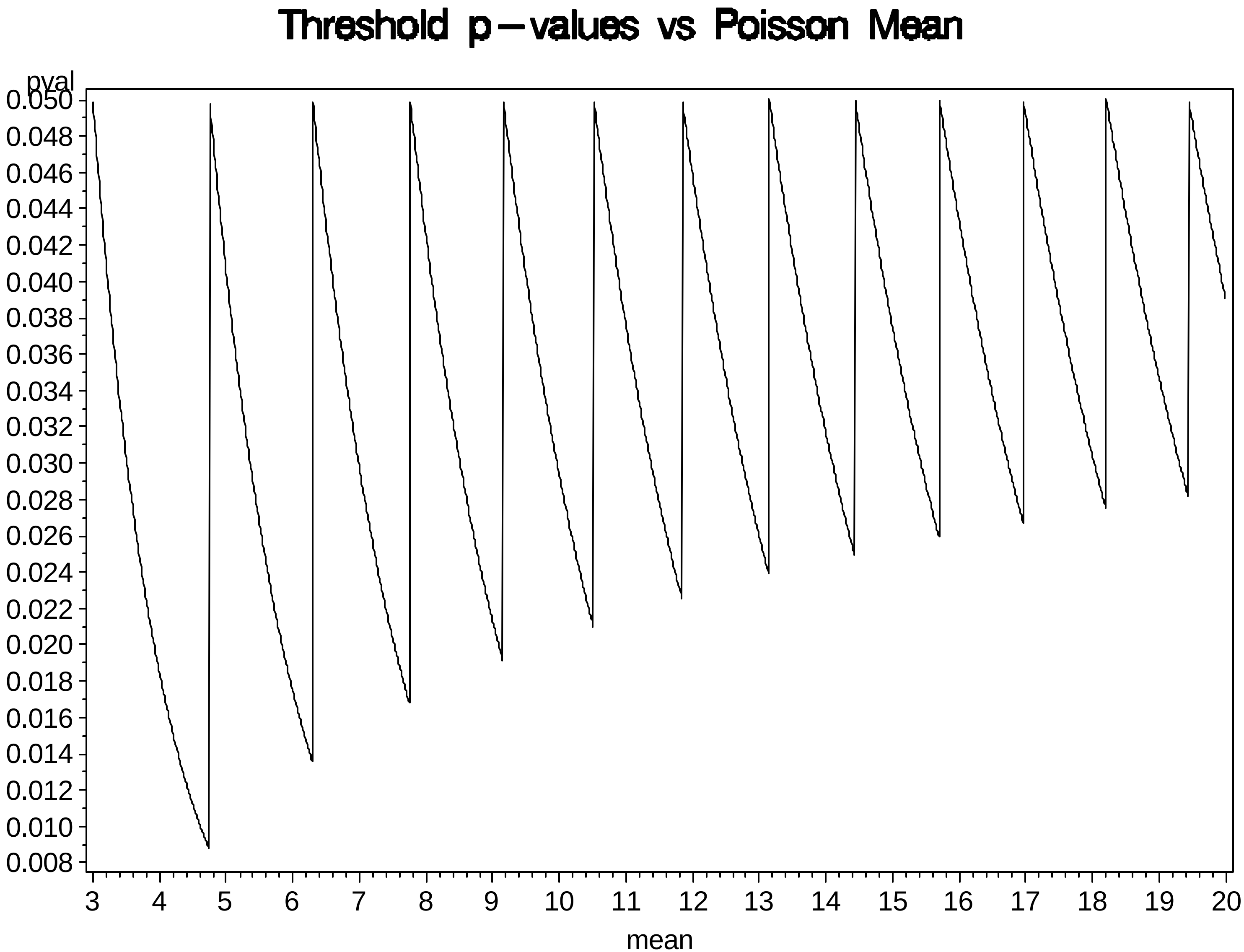
- Patients will be recruited continuously from clinics around the country.
- Upon entering the study they will be removed from their fluconazole regimens.
- Data will be kept on the number of person-years at risk observed and the number of recurrent cases observed.

Clinical Hypothesis

- Is the recurrence incidence density of cryptococcal meningitis less than 5 cases per 100 person-years at risk?”

Whitehead's Christmas Tree Adjustment




Threshold p-values vs Poisson Mean
pval
0.050
0.048
0.046
0.044
0.042
0.040
0.038
0.036
0.034
0.032
0.030
0.028
0.026
0.024
0.022
0.020
0.018
0.016
0.014
0.012
0.010
0.008
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17
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19
20
mean

CI For A Particular Alpha Estimate

Binomial outcome implies…

$$s^2 = \frac{p\left(1 - p\right)}{n} = \frac{0.038(0.962)}{2000} = 0.00002$$

$$0.038 \pm 1.96\sqrt{0.00002} = \left(0.029, 0.047\right)$$