Clinical Drug Development with a Bayesian Lens

Stephen J Ruberg, PhD
Advanced Analytics
Eli Lilly & Company
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Meg Gamalo
Karen Price
Scott Berry
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The Beginning is Always the Hardest
Key Question

What would it look like if SUBSTANTIAL EVIDENCE was based on a Bayesian posterior probability rather than p-value(s)?
Substantial Evidence

Pr (drug works) > threshold
Substantial Evidence


Drug – Placebo > 0

Pr (drug works) > threshold
Substantial Evidence

Drug – Placebo > CM

Pr (drug works) > threshold
Substantial Evidence

Drug – Placebo > Benefit-Risk

\[ \Pr (\text{drug works}) > \text{threshold} \]
Approval

Pr (drug works) > threshold

Disease
Common
Life-threatening
Rare disease
Unmet need
Approval

Pr (drug works) > threshold

Endpoints
Hard
Surrogate
Objective
Subjective
Approval

Hypothetical Examples

Pr (cure for pancreatic cancer) > 0.50

Pr (weight loss of 5kg) > 0.95

Pr (increased survival by 9 months) > 0.85
“FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet the statutory standards.”

21 C.F.R. § 314.105(c).
Phase 3
How much data?
Study Design
PRIOR
EoPh2 Meeting
Mechanistic Research

- IL-1β
- IL-6
- IL-23
- IL-21

INFAMMATORY CYTOKINES

Destabilize

T_h,17

T_REG

Effector cytokine

IL-17

Macrophage

Neutrophil

Endothelial cell

Fibroblast

Recruitment of inflammatory cells

Induction of inflammatory mediators

IL-21

NK cell

CD8^+ T cell

Cytotoxic differentiation

IL-22

Hepatocyte

Acute-phase reaction

CCL20

Dendritic cell

CCR6

Recruitment of dendritic and T cells
PK / PD Models

\[ ACR20 = \logit^{-1}(BL + (Amplitude \times time_{50})/(et50 + time_{50}), upper = 100, lower = 0) \]
Phase 2 Data
(or Phase 1 in some cases)

Use data from trials of same treatment as well as other treatments in the same class.
Robust Bayes

♦ Usual approach: for unknown parameter(s), $\theta$, specify ‘informative prior’ $\theta \sim \pi_I(\theta | \eta)$

♦ A ‘robust’ approach (just use a prior mixture):

$$\theta \sim \epsilon \cdot \pi_I(\theta | \eta_1) + (1 - \epsilon) \cdot \pi_R(\theta | \eta_2)$$

♦ Example:

$$\theta \sim .85 \cdot N(.52, .1) + .15 \cdot U(.1,2)$$
Limitations

♦ Shrinkage of Ph 2 results
♦ Network meta-analysis
  • How much data to include
  • How far back to go
♦ Changes in patient populations, geographies, doses, duration of treatment
♦ Changing endpoints (actual measure and the time of measurement)
Regulatory Considerations

♦ It’s different for everyone, but …

♦ Reward more robust Phase 2 programs
Phase 2
Clinically Meaningful Threshold
The most comprehensive survey of clinical success rates across the drug industry to date shows productivity may be even lower than previous estimates.
Regulatory Input or Not?
How many studies?
Reproducibility
Interim Analysis
See Brad Carlin’s presentation
Summary

From Comments on ASA Statement on p-values

(1) What does the data say?
   • P-values attempt to answer Q1, but they are not the best answer.

(2) What should I believe?
   • A likelihood function gives a richer depiction of evidence, and Bayesian methods formally answer Q2 with prior probability distribution to represent pre-data information or belief.

(3) What should I decide?
   • Q3 requires a loss function in addition to data.
Summary

Do simulations to assess characteristics of this system

See Scott Berry’s and Telba Irony’s presentations
Summary

Nowhere did I say “Alpha is …”
Summary

Making probability assessments (intuition, judgments) more explicit/quantifiable
Summary

ICH-E9
Pre-specification

• Bring objectivity, good science
• Minimize post hoc assessments
Conclusion

Where to start?

♦ Non-inferiority
♦ Pediatrics
♦ Anti-infectives
♦ Orphan drugs
♦ Breakthrough

See Telba Iony’s presentation
Conclusion

Fundamentally change the way we do business
Clinical Drug Development
with a
Bayesian Lens

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