A Conservative Approach to Leveraging Prior Evidence about Treatment Effects for Effective Group Sequential Clinical Trial Design

Image source: https://www.actiontohappyhealthywealthy.com/leverage-why-always-use/

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PSI conference 2024

Technical TED Talk – 8 minutes presentation

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I am not here to sell you anything

- This presentation does not necessarily reflect AstraZeneca's positions
- Should anything be unclear, feel free to ask for clarifications.
- Constructive criticism will also be appreciated.
- Should You wish to get in touch, I am on LinkedIn.

Applied Statistics is (almost) bilingual - Statistics Wars Are Useless

- Experimental design and analysis are meant to provide strong evidence about clear hypotheses
  - Conditional error probabilities are but a means to and end:

Pre-data odds of design hypotheses + Error probabilities = post-data odds of design hypotheses

2017

Comment | Published: 01 September 2017

Redefine statistical significance

Daniel J. Benjamin, James O. Berger, Magnus Johannesson, Brian A. Nosek, E.-J. Wagenmakers, Richard Berk, Kenneth A. Bollen, Björn Brembs, Lawrence Brown, Colin Camerer, David Cesarini, Christopher D. Chambers, Merlise Clyde, Thomas D. Cook, Paul De Boeck, Zoltan Dienes, Anna Dreber, Kenny Easwaran, Charles Efferson, Ernst Fehr, Fiona Fidler, Andy P. Field, Malcolm Forster, Edward I. George, ... Valen E. Johnson + Show authors

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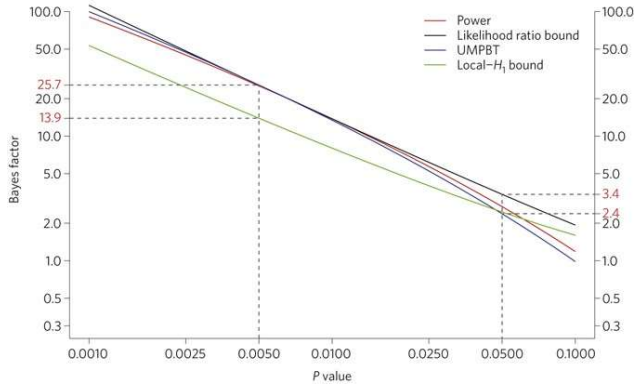
$$\frac{\Pr(H_1 \mid x_{\text{obs}})}{\Pr(H_0 \mid x_{\text{obs}})} = \frac{f(x_{\text{obs}} \mid H_1)}{f(x_{\text{obs}} \mid H_0)} \times \frac{\Pr(H_1)}{\Pr(H_0)} \equiv \text{BF} \times (\text{prior odds})$$



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A conservative approach to leveraging external evidence for effective clinical trial design

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$$\begin{cases} r_{10}(+) := \dfrac{P(H_1 \mid +)}{P(H_0 \mid +)} = \dfrac{P(H_1)}{P(H_0)} \times \dfrac{p(+ \mid H_1)}{p(+ \mid H_0)} \\ r_{01}(-) := \dfrac{P(H_0 \mid -)}{P(H_1 \mid -)} = \dfrac{P(H_0)}{P(H_1)} \times \dfrac{p(- \mid H_0)}{p(- \mid H_1)} \end{cases}$$

Example (Ph3): $\frac{P(H_0)}{P(H_1)} = 1$, 5% false positive, 90% power,

then : $r_{01}(-_3) = 0.95/0.1 = 9.5$

$r_{10}(+_3) = 0.9/0.05 = 18$

Effective CDP design targets clinical equipoise imbalance

- **Start**: Ph1 data shows safety and tolerability in target population (clinical equipoise)
- **Goals**: design randomized Ph2 *and* Ph3 trials providing strong evidence in favor of
  1. the Ph2 & Ph3 hypotheses $\{H_{1,2}, H_{1,3}\}$ vs their nulls $\{H_{0,2}, H_{0,3}\}$ when both trials are + $(+_2, +_3)$
  2. the trials null hypotheses when Ph2 trial is + but Ph3 is – $(+_2, -_3)$
- **CDP design metric**: post-trial odds of the CDP hypotheses vs null

$$\begin{cases} r_{10}(+_2,+_3) := \dfrac{P(H_{1,2},H_{1,3} \mid +_2,+_3)}{P(H_{0,2},H_{0,3} \mid +_2,+_3)} = \dfrac{p(+_2 \mid H_{1,2})}{p(+_2 \mid H_{0,2})} \times \dfrac{p(+_3 \mid H_{1,3})}{p(+_3 \mid H_{0,3})} > \dfrac{0.9}{0.05} = 18 \\ r_{01}(+_2,-_3) := \dfrac{P(H_{0,2},H_{0,3} \mid +_2,-_3)}{P(H_{1,2},H_{1,3} \mid +_2,-_3)} = \dfrac{p(+_2 \mid H_{0,2})}{p(+_2 \mid H_{1,2})} \times \dfrac{p(-_3 \mid H_{0,3})}{p(-_3 \mid H_{1,3})} \geq \dfrac{0.95}{0.1} = 9.5 \end{cases}$$

- **Note**: requiring <u>*both*</u> 1-2 to hold is <u>*hard*</u>, i.e. this CDP design requirement goes beyond current practice, to protect future patients from futile repetition of similar trials and it will inflate sample size.

Should negative evidence be an objective at all in clinical development?

Example- standard OCs provide strong positive evidence

- **Ph2**:
  - Open label, 1:1 RCT
  - Primary efficacy endpoint: ORR difference ($H_{1,2} \coloneqq ORR_{inv} = 75\%, ORR_{SOC} = 50\%$)
  - Single efficacy analysis, p-value +/- decision rule
- **Ph3**:
  - Double blind, 1:1 RCT
  - Primary efficacy endpoint: TTE HR ($H_{1,3} \coloneqq HR = 0.7, \text{median}_{SOC} = 10mo$)
  - GS design with 1 IA, OBF α spending function, p-values +/- decision rules, $p(+_3 | H_{0,3}) = 5\%$
- **CDP OCs** and overall odds of hypotheses at FA:

CDP strategy	N total	$p(+_2 \mid H_{0,2})$	$p(+_2 \mid H_{1,2})$	$p(+_3 \mid H_{1,3})$	$r_{10}(+_2, +_3)$	$r_{01}(+_2, -_3)$
Minimal	550	10%	80%	80%	134	0.6
Standard	680			90%	151	1.2
Robust	1170	5%	90%	99%	374	4.8

Is positive evidence achieved by these methods too much?

Thank you for your attention.

Q&A