Beyond Lalonde

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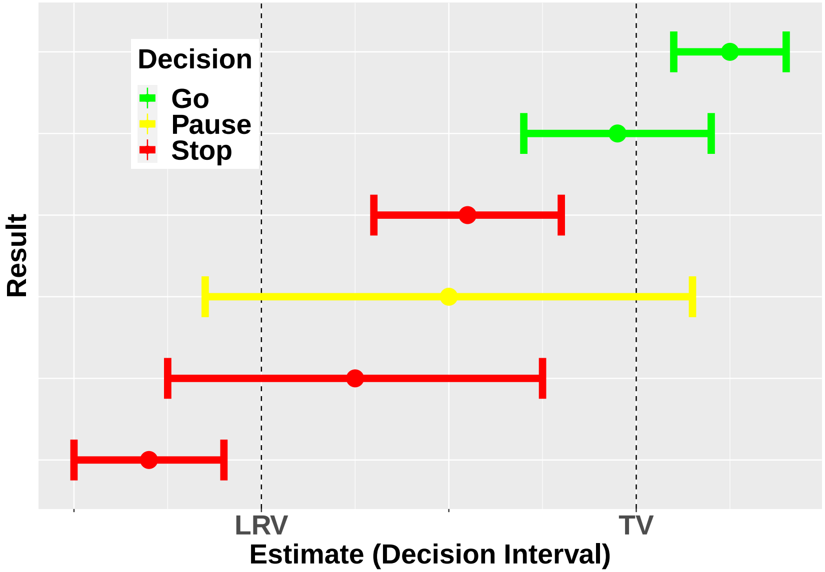
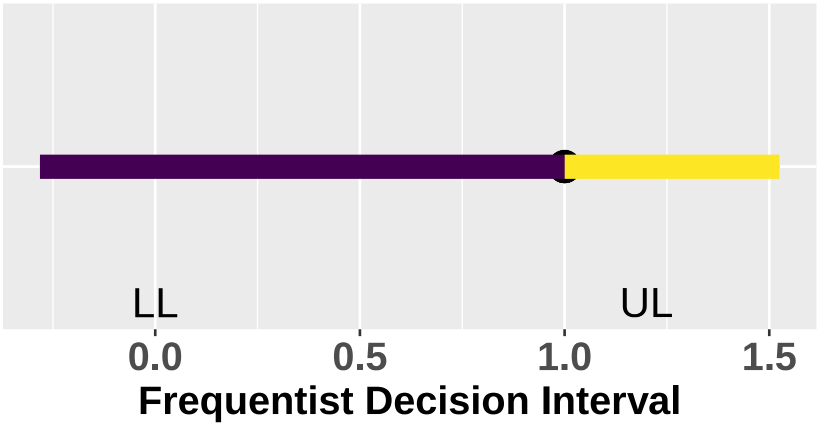
Dual Criterion Decision Criteria



(Lalonde et al. 2007)

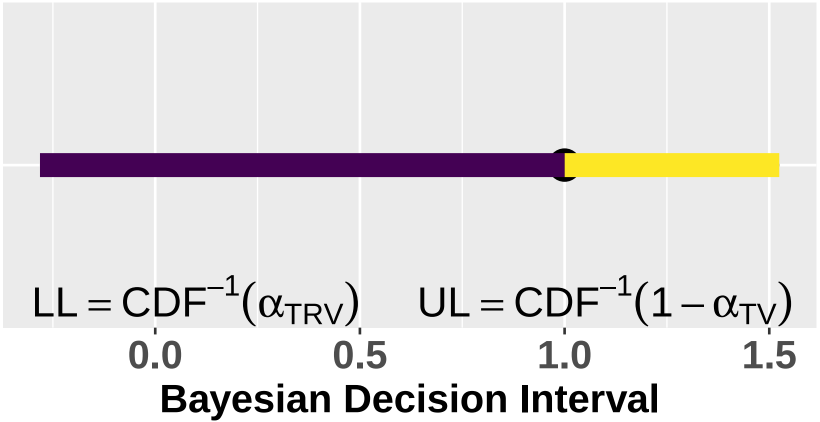
The Criterion - Frequentist



Two "halves" of different one sided $\frac{1}{2}$ confidence intervals glued together, with one based on α_{LRV} and the other on α_{TV}.

(Chuang-Stein and Kirby 2017) denotes LPDAT with no reference

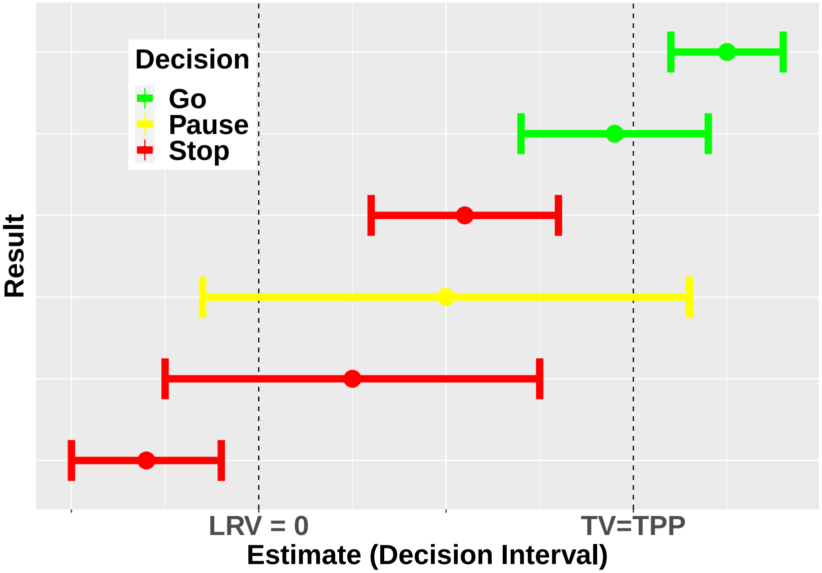
The Criterion - Bayesian



CDF is the cumulative distribution function of the posterior distribution of μ.

Bayesian approach offers intuitive decision rules and eases incorporation of external information.

Graphical Criteria - LRV is 0



Decision criteria - LRV is 0

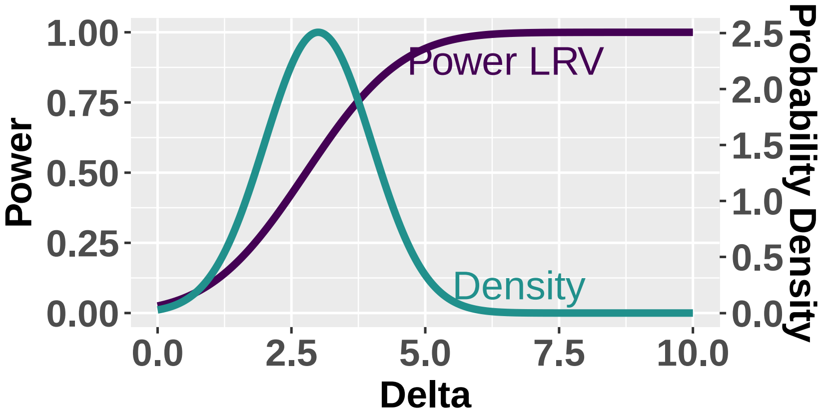
Frequentest:

- LL $>$ LRV and UCI $>$ TV, then Go.
- LL $\leq$ LRV and UCI $>$ TV, then Pause.
- UCI $\leq$ TV, then Stop.

Bayesian:

- Prob($\mu >$ LRV) $> \alpha_{TRV}$ and Prob($\mu >$ TV) $> 1 - \alpha_{TV}$, then Go.
- Prob($\mu >$ LRV) $\leq \alpha_{TRV}$ and Prob($\mu >$ TV) $> 1 - \alpha_{TV}$, then Pause.
- Prob($\mu >$ TV) $\leq 1 - \alpha_{TV}$, then Stop.

Aside - Assurance

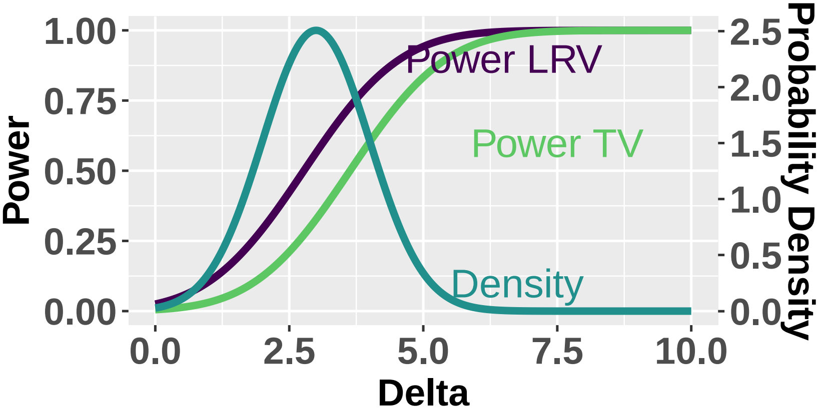


Assurance, or Average Power

1. Posterior
2. Power (ie phase 3 design) of some statistical test.

(Spiegelhalter and Freedman 1986), (O'Hagan, Stevens, and Campbell 2005)

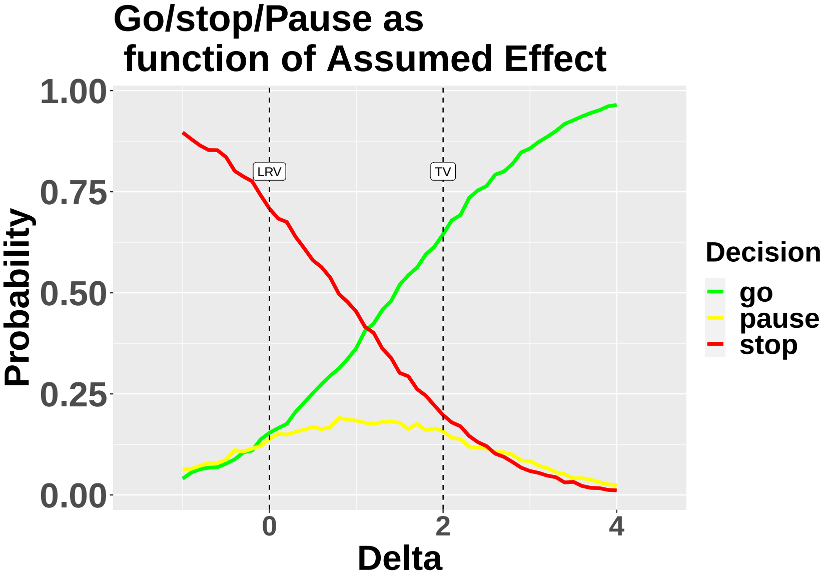
The Criterion - Assurance



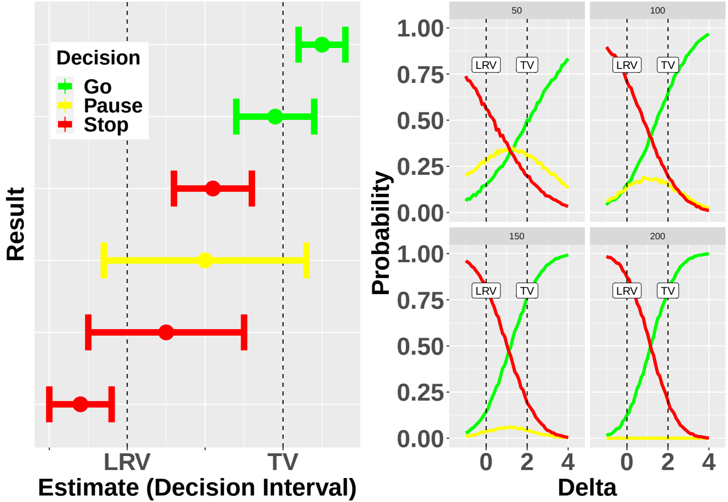
1. Assurance that statistical test will be successful in phase 3 meets some threshold.
2. Assurance that failing to reject greater than TV for some α) meets some threshold.

If both 1 and 2 are met, go. If only 2 is met pause, and if 2 is not met then stop. Suggested by Mark Heize, at CSL Behring.

Operating Characteristics - Conditional Probabilities

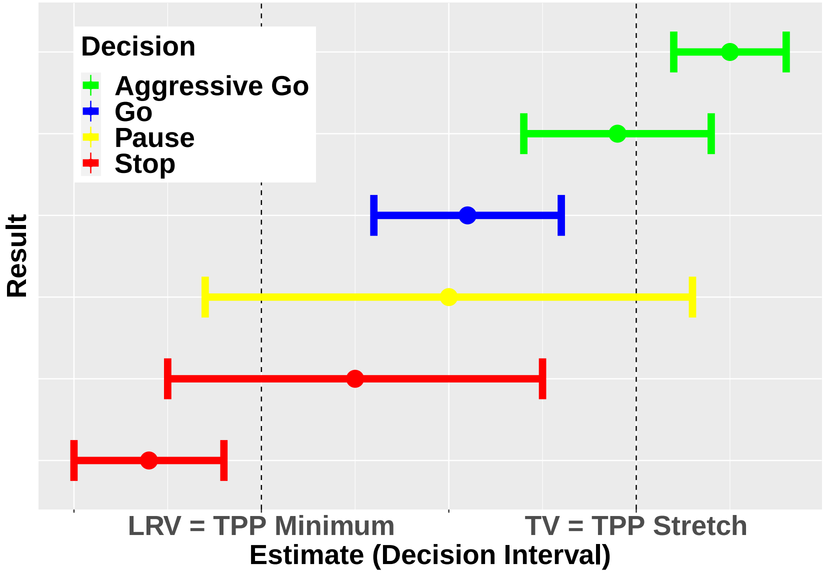


Conditional Operating Characteristics - LRV = 0

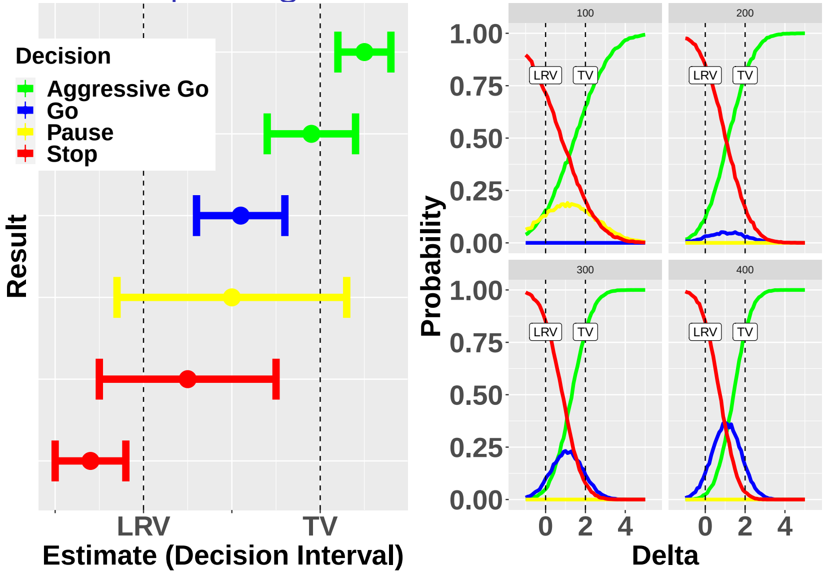


- Understand ahead of time what other information may drive a decision when results are "Pause"
- Is "Pause" an opportunity for an adaptive sample size change?

Graphical Criteria - LRV = minimal TPP

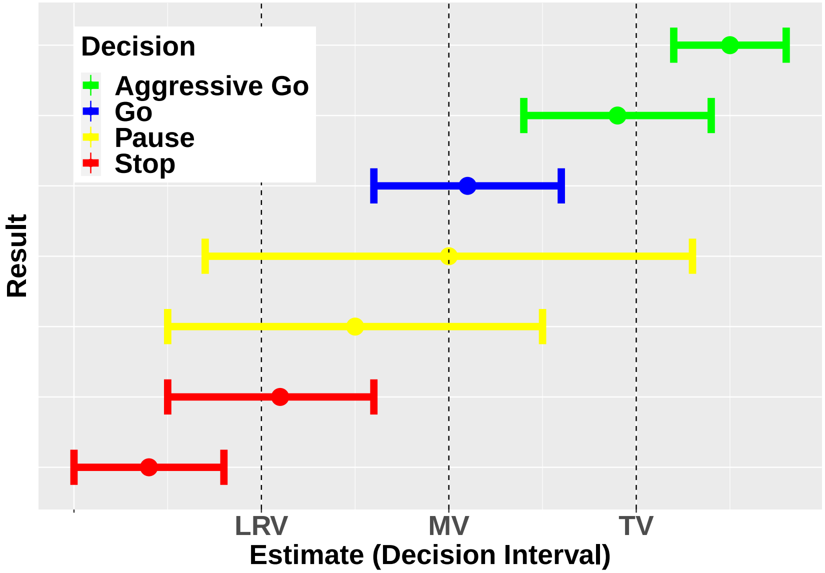


Conditional Operating Characteristics - LRV = min TPP



This requires large α for LRV, or huge effect. (Chuang-Stein et al. 2011)

Graphical Criteria - Considering 3 criteria

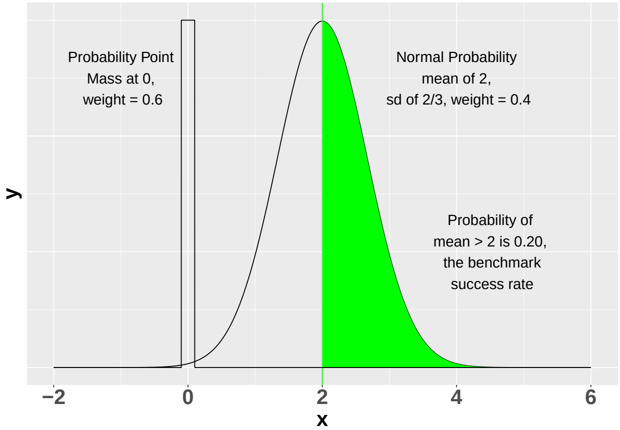


Incorperating external information

Bayesian and Assurance versions could include prior information.

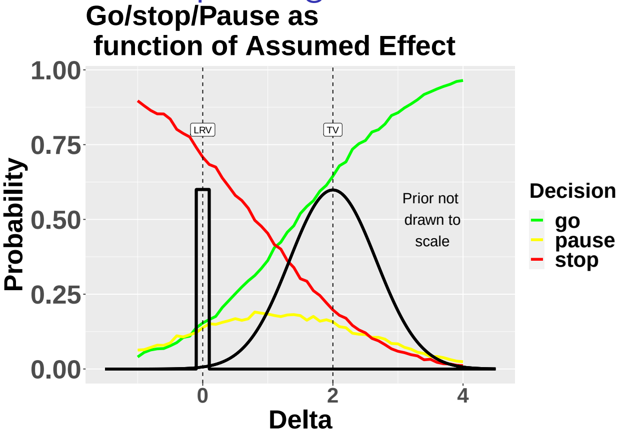
1. Used to reduce sample size in the context of decision rules - historic information on comparator, prior elicitation, PK/PD modeling, etc.(ref)
2. Temper your enthusiasm. Include pessimistic historic prior based on benchmark probability of success.

Spike and Smear Prior for Benchmark POS



(Chuang-Stein and Kirby 2017)

Unconditional operating characteristics



Assurance can be used as unconditional operating characteristics of the probability of Go, Pause and Stop. (Spiegelhalter and Freedman 1986)

Probability of Go conditional on No Go decision
Probability of Go conditional on a Go decision

Example unconditional operating characteristics

	Truth			
Decision	Stop	Pause	Go	Total
Go	0.10	0.03	0.22	0.34
Pause	0.08	0.01	0.04	0.13
Stop	0.44	0.03	0.06	0.52
Total	0.62	0.07	0.31	1.00

Probability of a True Go conditional on Go decision $= \frac{0.22}{0.34} = 0.65$

Caveat on Design

If focus is solely on operating characteristics, and limiting sample size, teams may manipulate alphas.

The larger the α used for TV, the more confidence you will have in meeting TV. The smaller the α used for LRV, the more confidence you will have in the existance a treatment effect.

Optimizing Drug Development Process

Recent work examines optimizing sample size of phase 2 for overall probability of success

- (Jiang 2011) From an Assurance standpoint
- (De Martini 2013) Looking at this for a long time, mostly working in frequentist setting
- (Pulkstenis, Patra, and Zhang 2017) Does this in a Bayesian framework for Lalonde framework

(Dmitrienko and Pulkstenis 2017)

Challenges of POC

Decision making does not make poor performing drugs perform better!

1. Good decision making (Chuang-Stein and Kirby 2017)
2. Good design considering Decision Bias due to decision making (Kirby et al. 2012)
3. Utility optimization over both 1 and 2. (Preussler, Kieser, and Kirchner 2019)

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