Decision making that would make Frank Harrell and Stephen Senn tweet

DSBS 30th Anniversary/2022 General meeting

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April 29th, 2022

Dermatology
beyond the skin

LEO

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The views expressed herein represent those of the presenter and do not necessarily represent the views or practices of LEO Pharma A/S.

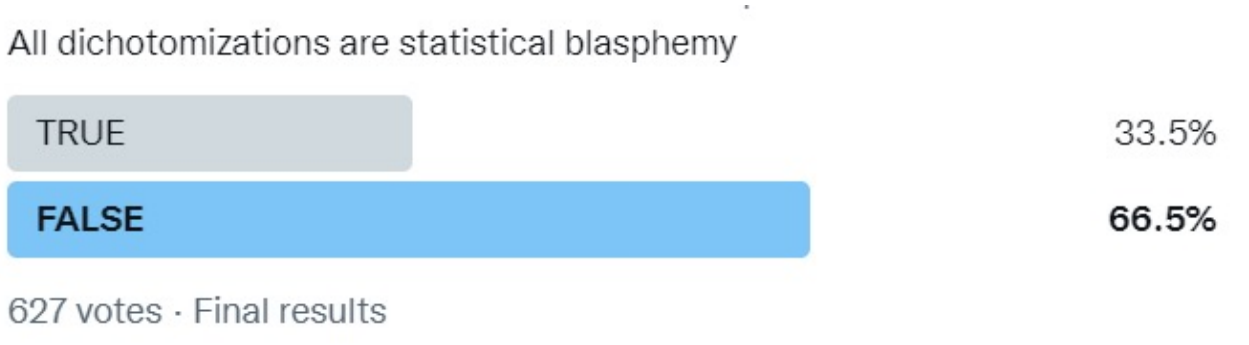
So what do Stephen Senn and Frank Harrell tweet about?

Common themes

I. The inefficiency of dichtomizing continuous endpoints

II. The perils of using percent change/change scores

III. Advocating for the use of ordinal regression models when analyzing ordinal data



So what do we do in dermatology?

- Phase 3 clinical trials for dermatological indications such as psoriasis and atopic dermititis, typically include two co-primary endpoints: EASI/PASI-75 and vIGA-AD/IGA 0/1

- EASI (Eczema Area and Severity Index) is an ordinal scale ranging from 0-72

- Despite being an ordinal scale, typical endpoints include:

  - the change from baseline in EASI score at wk 12/16
  - percent change from baseline in EASI score at wk 12/16
  - percent change from baseline in EASI score exceeding a specific threshold, e.g. 50%/75%/90%/100% at wk 12/16

- vIGA-AD is a 5 point ordinal scale, ranging from 0-Clear to 4-Severe

- IGA 0/1 is binary endpoint assessing whether a subject achieved an IGA score of either 0 or 1 at wk 12/16

The trials and tribulations of introducing a Go/No-Go decision framework for early clinical trials at LEO Pharma

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Overview

- Stigmas to overcome
- The initial Go/No Go framework for phase 2A studies
- Lesson 1: Motivating the selection of a suitable threshold
- Lesson 2: Non-informative vs. Goldilocks priors
- Lesson 3: Understanding your customers motives/wishes

Stigmas/resistance to overcome

" A final stop/go recommendation will in all cases be based on both efficacy and safety, and may include additional analyses if results are borderline"

"Wouldn't it be better to use a continuous endpoint, such as (percent) change from baseline? What happens if a couple of subjects fall just short of the responder threshold of a 75% change from baseline?"

"Isn't the threshold to low?"

Initial Go/No-Go framework

- The framework aims to assess the probability of exceeding the minimum business case threshold for EASI-75 and vIGA-AD 0/1 at week 16, as specified in the target product profile, (minTPP).

- To do this, we will implement a Bayesian framework

- Let θ_{Active} and $\theta_{Placebo}$ represent the EASI-75 response rates at week 16

- Assume non-informative prior distributions for θ_{Active} and $\theta_{Placebo}$, i.e

$$\pi_i(\theta) \sim Beta(\alpha = 1, \beta = 1), \qquad i \in \{Active, Placebo\}$$

- The posterior distributions,

$$\pi_i(\theta|r_i) \propto p(r_i|\theta)\pi_i(\theta) \sim Beta(\alpha = 1 + r_i, \beta = 1 + n_i - r_i)$$

Initial Go/No-Go framework

- The posterior probability of exceeding the minimum TPP threshold, $\mathbf{minTPP}$, can then be expressed as an integral,

$$\int_0^{1-minTPP} \Pr(\theta_{Active} > p + minTPP) f_{Placebo}(p) dp$$

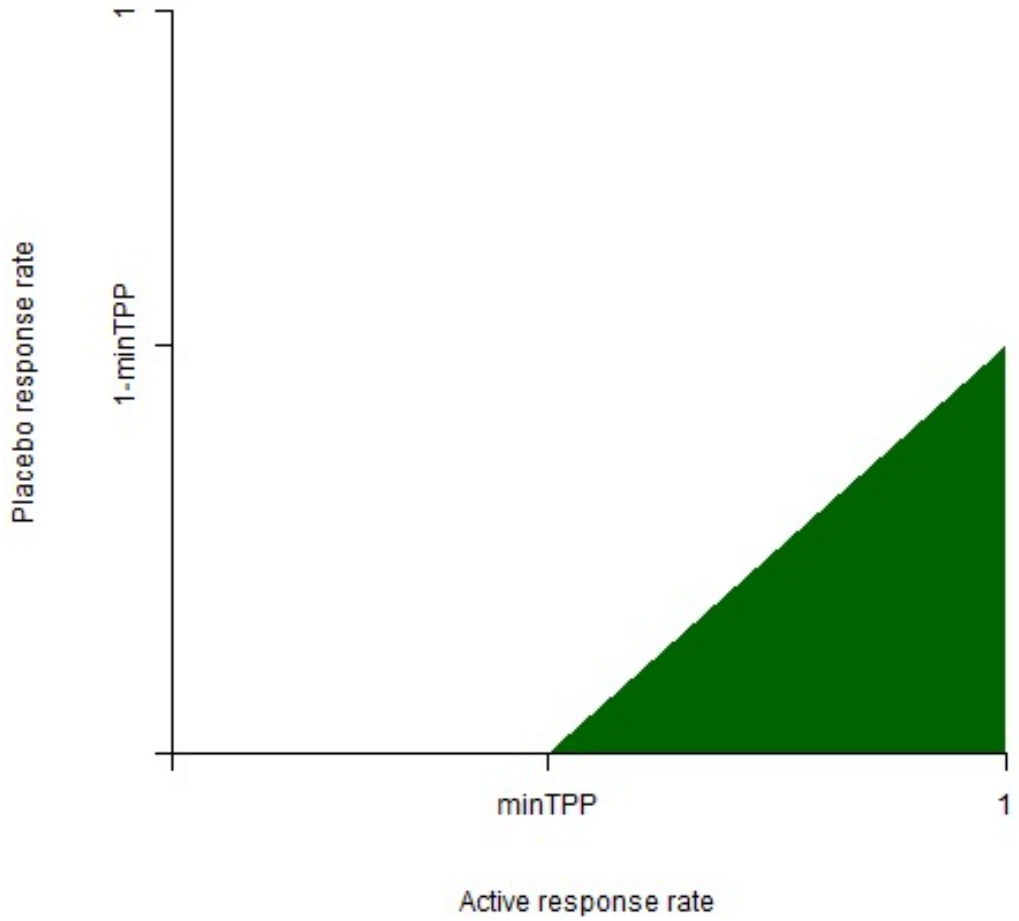
- Easily assessed using the R package, RBesT

Example: N=(24,12), r=(16,1) and minTPP=45%

```
library(RBesT)
uniform_prior <- mixbeta(c(1,1,1))
active_posterior <- postmix(uniform_prior,n=24,r=16)
placebo_posterior <- postmix(uniform_prior,n=12,r=1)
pmixdiff(active_posterior,placebo_posterior,0.45,lower.tail=FALSE)
```

Implying that under the posterior distribution,

$$\Pr(\theta_{Active} - \theta_{Placebo} > 0.45) \approx 70.2\%$$



Initial Go/No-Go framework

- May also want to present the likelihood of exceeding the minimum, base and target thresholds

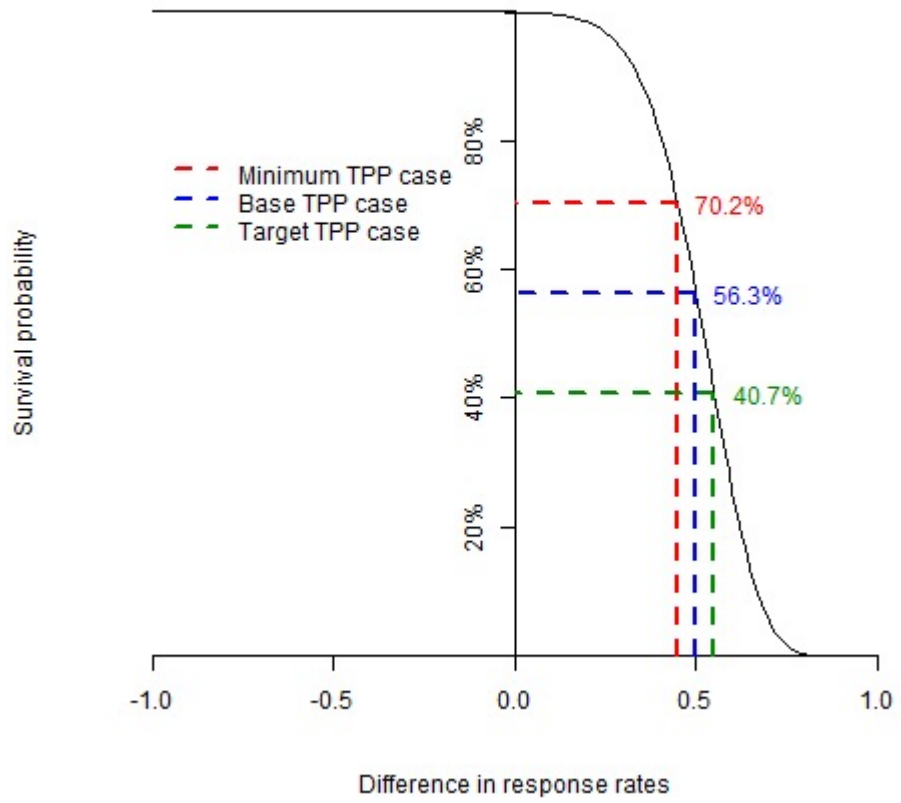
```
library(RBesT)
uniform_prior <- mixbeta(c(1,1,1))
active_posterior <- postmix(uniform_prior,n=24,r=16)
placebo_posterior <- postmix(uniform_prior,n=12,r=1)
survF <- pmixdiff(active_posterior,placebo_posterior,seq(-
1,1,0.01),lower.tail=FALSE)

plot(x=seq(-
1,1,0.01),y=survF,bty="n",axes=FALSE,type="l",col="black",xlab="Difference in
response rates",
    ylab="Survival probability")
axis(side=1,pos=c(0,-1))
axis(side=2,pos=c(0,0),at=seq(0,1,0.2),labels=c("","20%","40%","60%","80%",""))
segments(x0=0.45,x1=0.45,y0=0,y1=survF[146],lty=2,lwd=2,col="red")
segments(x0=0.45,x1=0,y0=survF[146],y1=survF[146],lty=2,lwd=2,col="red")
text(x=0.6,y=survF[146],labels=paste(round(survF[146]*100,digits=1),"%",sep=""),co
l="red")

segments(x0=0.5,x1=0.5,y0=0,y1=survF[151],lty=2,lwd=2,col="blue")
segments(x0=0.5,x1=0,y0=survF[151],y1=survF[151],lty=2,lwd=2,col="blue")
text(x=0.65,y=survF[151],labels=paste(round(survF[151]*100,digits=1),"%",sep=""),c
ol="blue")

segments(x0=0.55,x1=0.55,y0=0,y1=survF[156],lty=2,lwd=2,col="green4")
segments(x0=0.55,x1=0,y0=survF[156],y1=survF[156],lty=2,lwd=2,col="green4")
text(x=0.7,y=survF[156],labels=paste(round(survF[156]*100,digits=1),"%",sep=""),co
l="green4")

legend(x=-1,y=0.8,legend=c("Minimum TPP case","Base TPP case","Target TPP
case"),col=c("red","blue","green4"),lwd=2,lty=2,bty="n")
```



Lesson 1: Motivating the selection of a suitable threshold

- In order to make a decision, we need to select a suitable threshold, δ, such that under the posterior distribution,

$$\begin{cases} \Pr(\theta_{Active} - \theta_{Placebo} > minTPP) > \delta \rightarrow Go \\ \Pr(\theta_{Active} - \theta_{Placebo} > minTPP) \leq \delta \rightarrow Stop \end{cases}$$

- One way to motivate the selection of a threshold is through the use of a ROC curve comparing the TPR vs FPR

- Let $A = \{(r_{Active}, r_{Placebo}) | \Pr(\theta_{Active} - \theta_{Placebo} > minTPP) > \delta\}$, for some threshold δ. Then,

$$TPR = PR(A|\theta_{Active} - \theta_{Placebo} > minTPP)$$

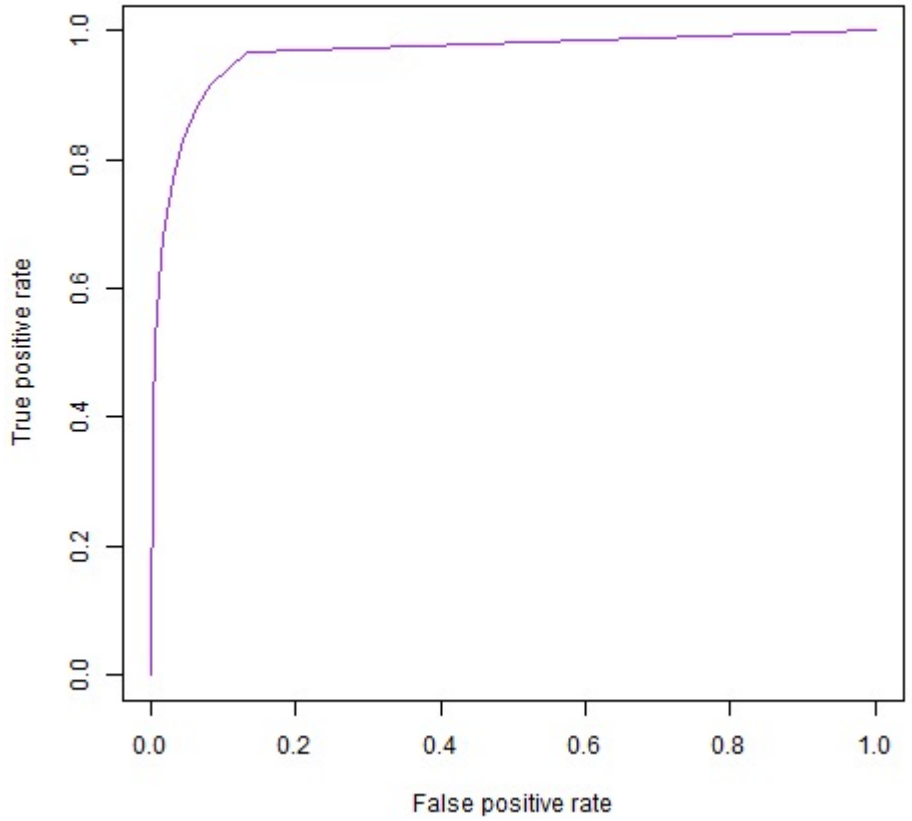
Lesson 1 cont.

Using Bayes formula, the TPR can be re-expressed as

$$\sum_{a \in A} \frac{Pr(\theta_{Active} - \theta_{Placebo} > minTPP | A = a) \Pr(A = a)}{Pr(\theta_{Active} - \theta_{Placebo} > minTPP)}$$

- Weighted average of the posterior probabilities of exceeding the minTPP for the outcomes in A
- Weights are normalized by the PoS (also referred to as assurance or expected power)

ROC curve for $N_1 = 24,\ N_2 = 12$ and minTPP = 45%. Minimizing the FPR while ensuring a TPR > 80% implies $\delta \approx 40\%$.



So what is the PoS?

- In the planning stages of a study, the PoS can be obtained by taking the expectation of the power function w.r.t. to the prior distributions

$$PoS = \int P(A|\boldsymbol{\theta})\,\pi(\boldsymbol{\theta})d\boldsymbol{\theta}$$

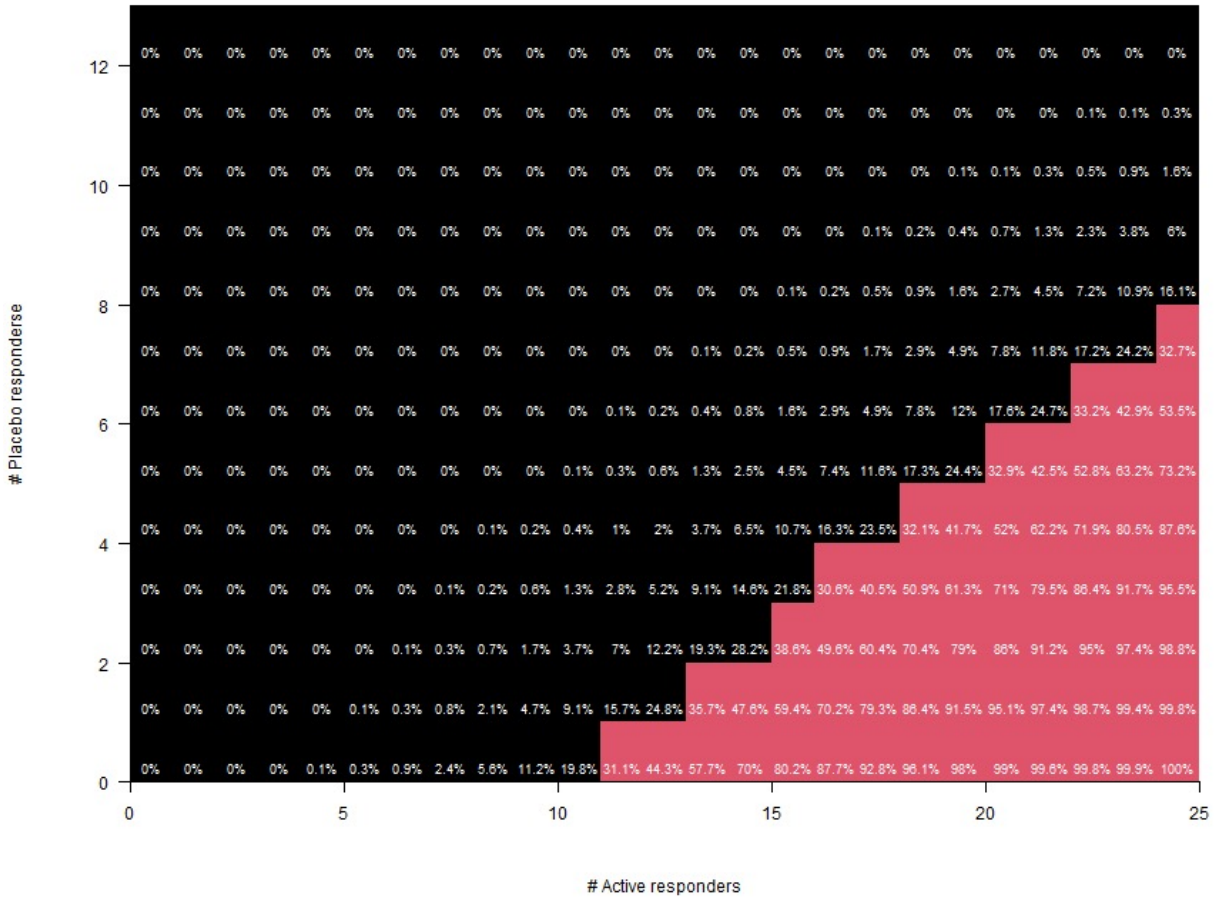
For our example with $N_1 = 24$, $N_2 = 12$ and $\delta = 0.3$,

$$A = \{(r_{Active}, r_{Placebo}) | \Pr(\theta_{Active} - \theta_{Placebo} > 0.45) > 0.3\}$$

The PoS can also be expressed in terms of the prior predictive distribution as

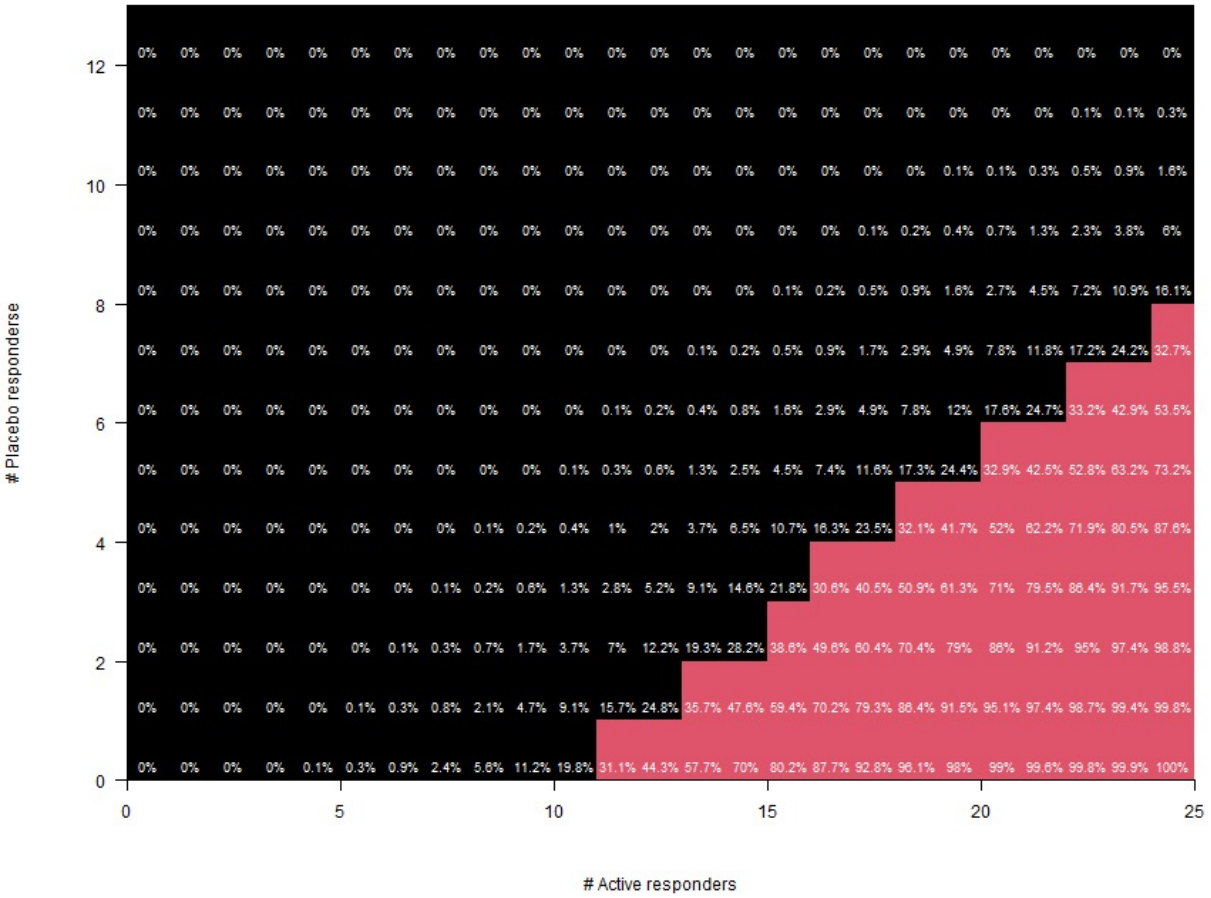
$$PoS = \sum_{(r_{Active}, r_{Placebo}) \in A} P(r_{Active}, r_{Placebo})$$

```
library(RBesT)
uniform_prior <- mixbeta(c(1,1,1))
decision <- decision2S(pc=0.3,qc=0.45,lower.tail=FALSE)
PoS_function <- pos2S(uniform_prior,uniform_prior,n1=24,n2=12,decision)
PoS_function(uniform_prior,uniform_prior)
```

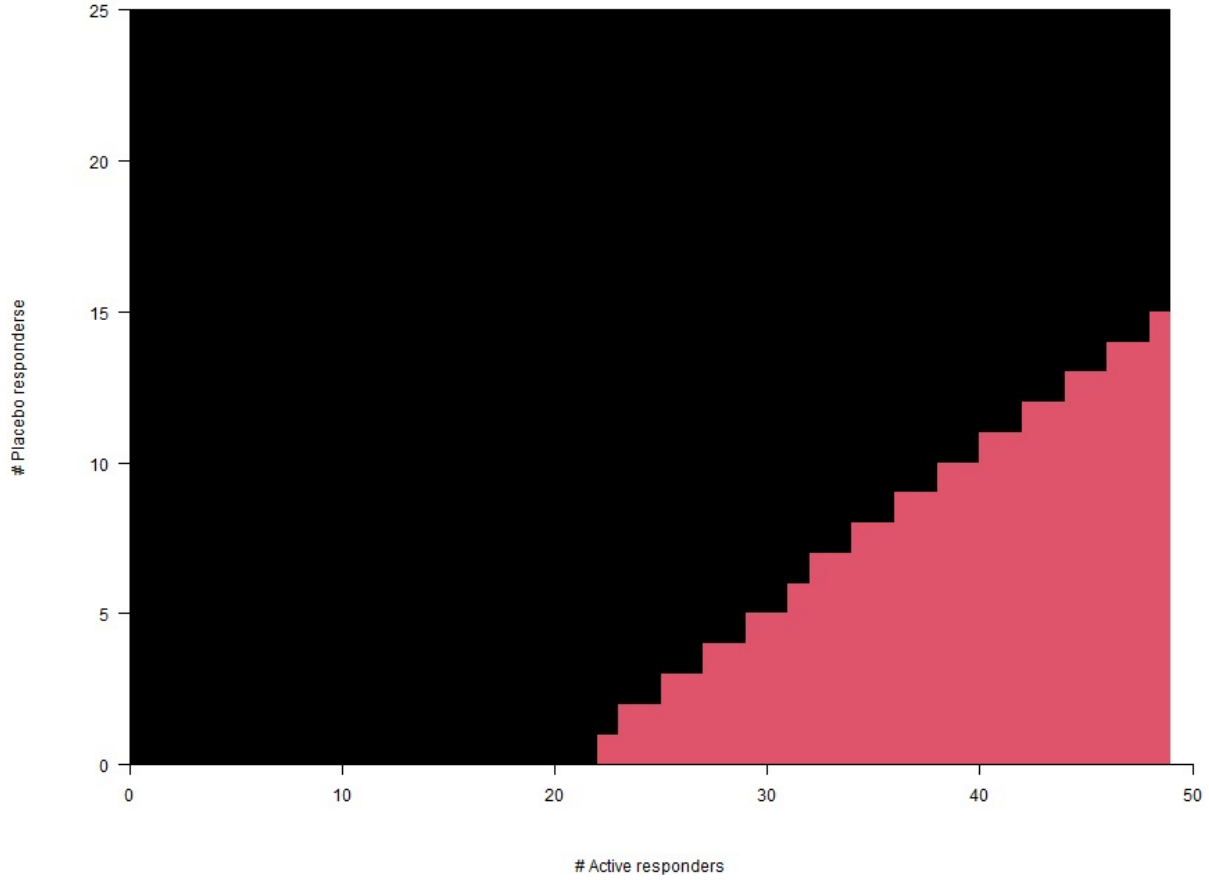


If we double the sample size of our example, the PoS actually decreases…

Posterior probabilities of exceeding the minTPP when $N_1 = 24$ and $N_2 = 12$ is 18.8%



Posterior probabilities of exceeding the minTPP when $N_1 = 48$ and $N_2 = 24$ is 17.8%



Perhaps the question we should be asking is what is the conditional assurance for the subsequent trials?

- Temple and Robertson, 2021 introduced the concept of conditional assurance

- The underlying premise, is to quantify the impact, a positive result from an early phase trial would have, on the overall PoS of a development program

- For example, the "design" posterior distribution obtained from a phase 2A study could be used to assess the PoS of future trials or the development program in general.

The conditional assurance can be used to:

I. Assess how succeeding in early stage trials affects the risk profile of the development program

II. Select a design for the planned study so that the risk profile of the development program aligns with the company's risk appeitite (e.g. selecting a decision threshold)

III. Used to develop a framework for optimizing the design of the planned study in terms of the eNPV

The conditional assurance framework

- Let $\pi_D(\boldsymbol{\theta})$ represent the "design" prior for the currently planned study, e.g. Our trial with $N_1 = 24$ and $N_2 = 12$

- Let

$$A_1 = \{(r_{Active}, r_{Placebo}) | \Pr(\theta_{Active} - \theta_{Placebo} > 0.45) > 0.3\}$$

and

$$A_2 = \{(r_{Active}, r_{Placebo}) | \Pr(\theta_{Active} - \theta_{Placebo} > 0.45) > 0.975\}$$

represent the events, that we achieve our pre-defined success criterion for the planned trial and the subsequent trial, respectively

- The "design" posterior from our planned trial can then be expressed as:

$$\pi_D(\boldsymbol{\theta}|A_1) = \frac{\Pr(A_1|\boldsymbol{\theta})\pi_D(\boldsymbol{\theta})}{\int \Pr(A_1|\boldsymbol{\theta})\pi_D(\boldsymbol{\theta})d\boldsymbol{\theta}}$$

- The conditional assurance is given by:

$$Pr(A_2|A_1) = \int \Pr(A_2|\boldsymbol{\theta})\, \pi_D(\boldsymbol{\theta}|A_1)d\boldsymbol{\theta}$$

Example

- Compare the conditional assurance for two competing designs:

  I. $N_1 = 24$ and $N_2 = 12$

  II. $N_1 = 48$ and $N_2 = 24$

with success criterion,

$$A_1 = \{(r_{Active}, r_{Placebo}) | \Pr(\theta_{Active} - \theta_{Placebo} > 0.45) > 0.3\}$$

- Assume the subsequent trial is a phase 3 trial with $N_1 = 400$ and $N_2 = 200$ subjects respectively and the following success criterion,

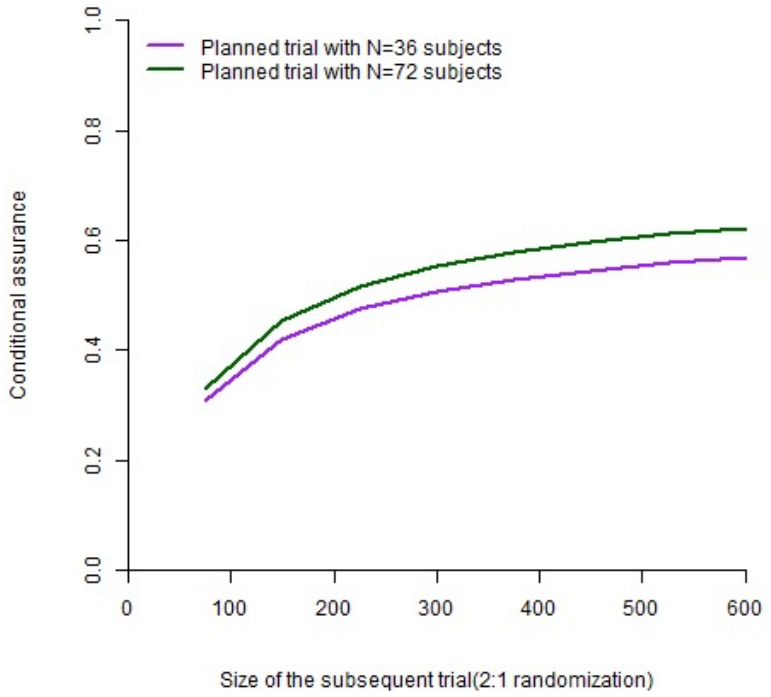
$$A_2 = \{(r_{Active}, r_{Placebo}) | \Pr(\theta_{Active} - \theta_{Placebo} > 0.45) > 0.975\}$$

- The conditional PoS for these two designs are:

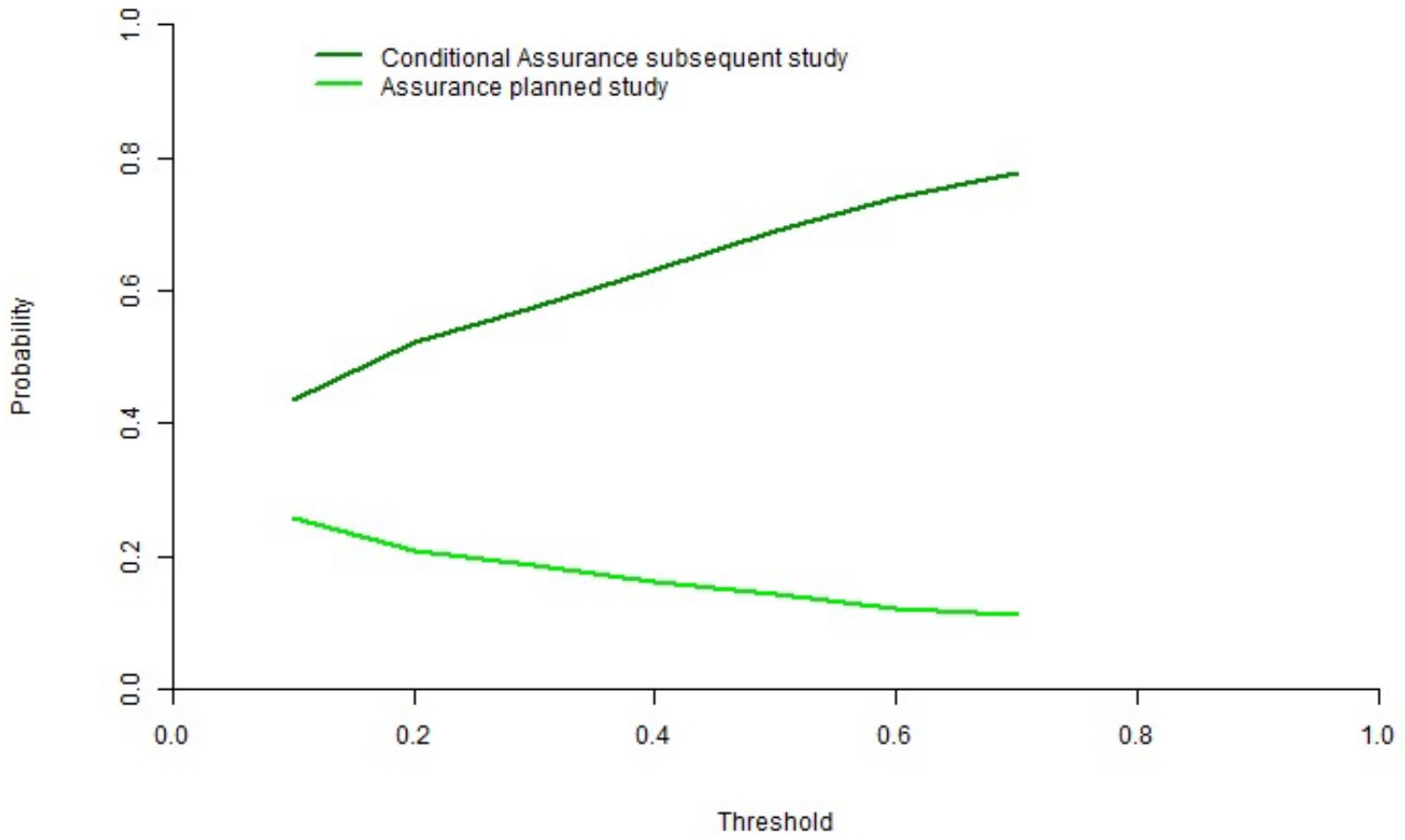
  I. 56.8%

  II. 62.4%

The conditional assurance as a function of the size of the subsequent trial



Motivating the selection of a threshold based on conditional assurance

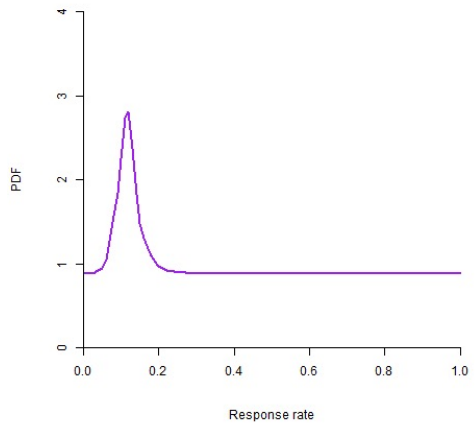


Lesson #2: Non-informative vs Goldilocks priors

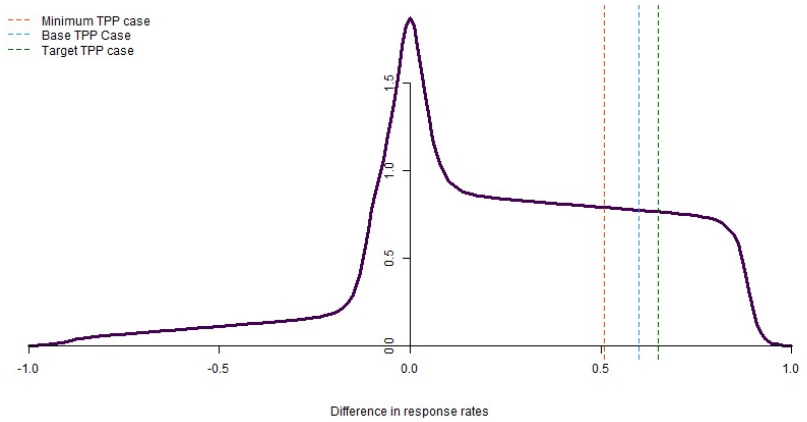
- For conditions such as psoriasis and AD, historical data exists from RCTs with similar patient populations
- The meta-analytic predictive (MAP) prior framework, introduced by Neuenschwander, et al, 2010 and further discussed by, Schmidli, et al., 2014, can be used to incorporate such historical data
- Such MAP priors can be "robustified" by mixing the MAP prior with a non-informative component
- The prior distribution for the active arm can be written as a bimodal mixture of the MAP prior and a component that either assumes the drug is efficacious, e.g. inline with the specified TPP or perhaps even a non-informative component.
- The weight attributed to each component can be derived by calibrating the PoS with the historical average for development programs at the same stage.

How to specify the prior distribution for the active arm

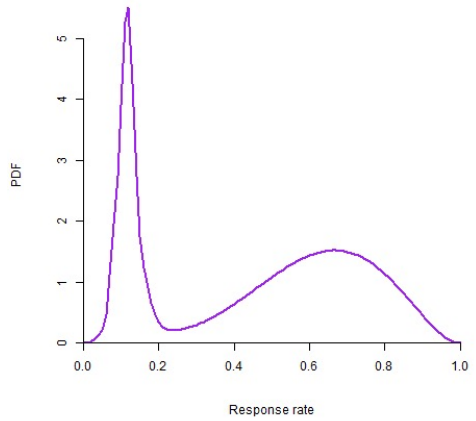
Prior distribution for the active arm by mixing the MAP prior and non-informative component



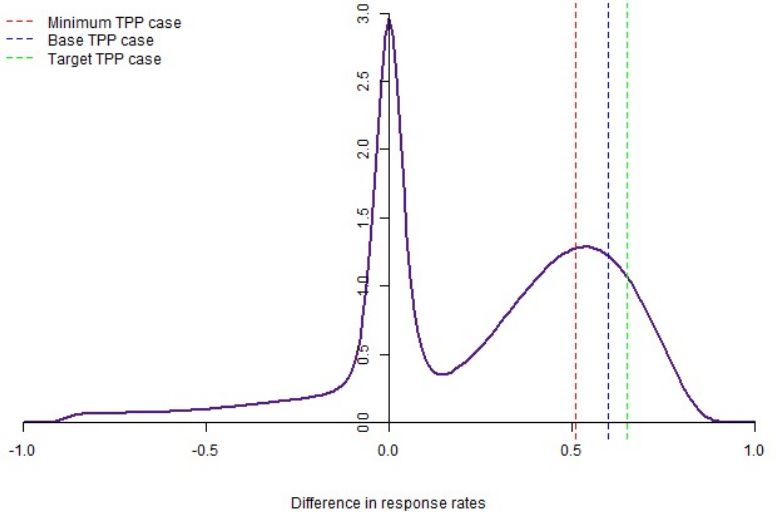
Implied prior distribution for the difference in response rate



Prior distribution for the active arm by mixing the MAP prior and phase 1b data



Implied prior distribution for the difference in response rate



Lesson #3: Understanding your customer

- LEO's current pipeline is "fairly healthy" and given our limited resources, a method for selecting the "most promising" candidate to take to phase 3 is needed.

- Current Go/No-Go framework, is designed for making "Gate decisions" not comparing development programs.

- Optimal criteria for such decisions would account for PoS of the development and the potential business case

- Assessing the eNPV, based on a PoS calculation using the framework presented in Hampson et al. 2022 seems like an ideal path forward!

References

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Thank you!

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