Statistical Go/NoGo in Early Clinical Development

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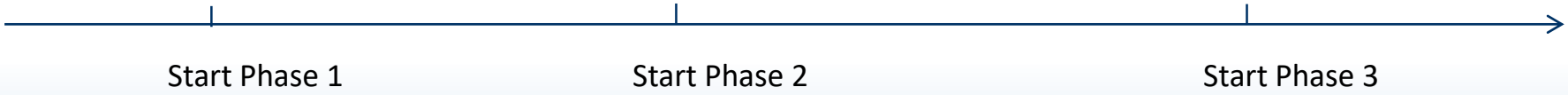
July 26, 2018

- *The views expressed in this presentation are my personal opinions and not those of Boehringer Ingelheim Pharmaceuticals, Inc.*

Introduction

- Decision making in clinical development



- Statistical Go/NoGo criteria
  - ***Pre-defined***, ***quantifiable*** criteria to allow for decision making given the trial results
    - Pre-defined in clinical development plan
  - Quantified risk assessment based on cumulative evidence using Bayesian approach
  - Environment: major pharma companies have implemented statistical Go/NoGo in early development

Background

- Early trials are short with small N
- Usually PD or surrogate endpoint measured for efficacy
- Safety signaling may be limited
- Decision errors:
  - False Go
  - False NoGo
- Standard type I and type II errors may be too strict.
- What about other sources of data (real world, registry etc)?

Risks with decision making

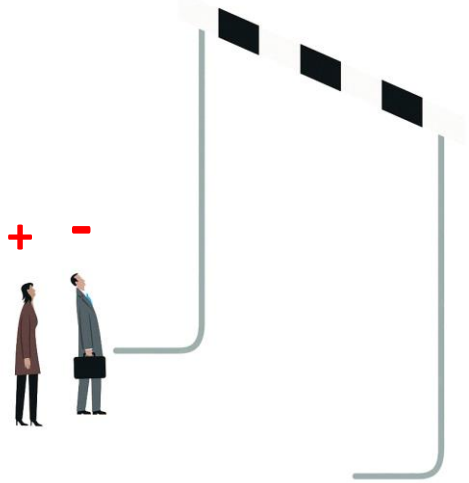
- Stop an effect drug (false NoGo)
- Move forward a non-effective drug (false Go)

	Go	NoGo
+	✓	False NoGo
-	False Go	✓

- Quantify the risks
  - ✓ P(false NoGo | +)
  - ✓ P(false Go | -)
  - ✓ Specify the assumptions associated with an effective or non-effect drug

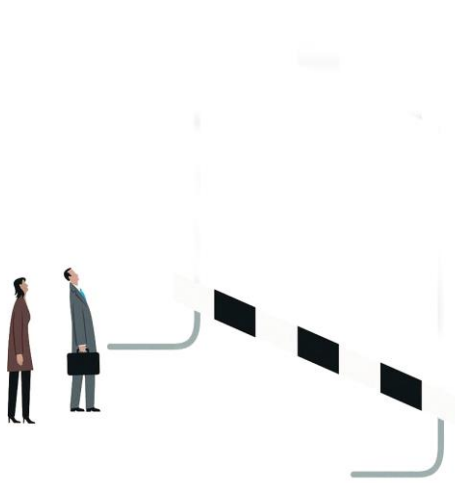
Set Go/NoGo criteria

High bar
- P(false NoGo| +) high
- P(false Go| -) low

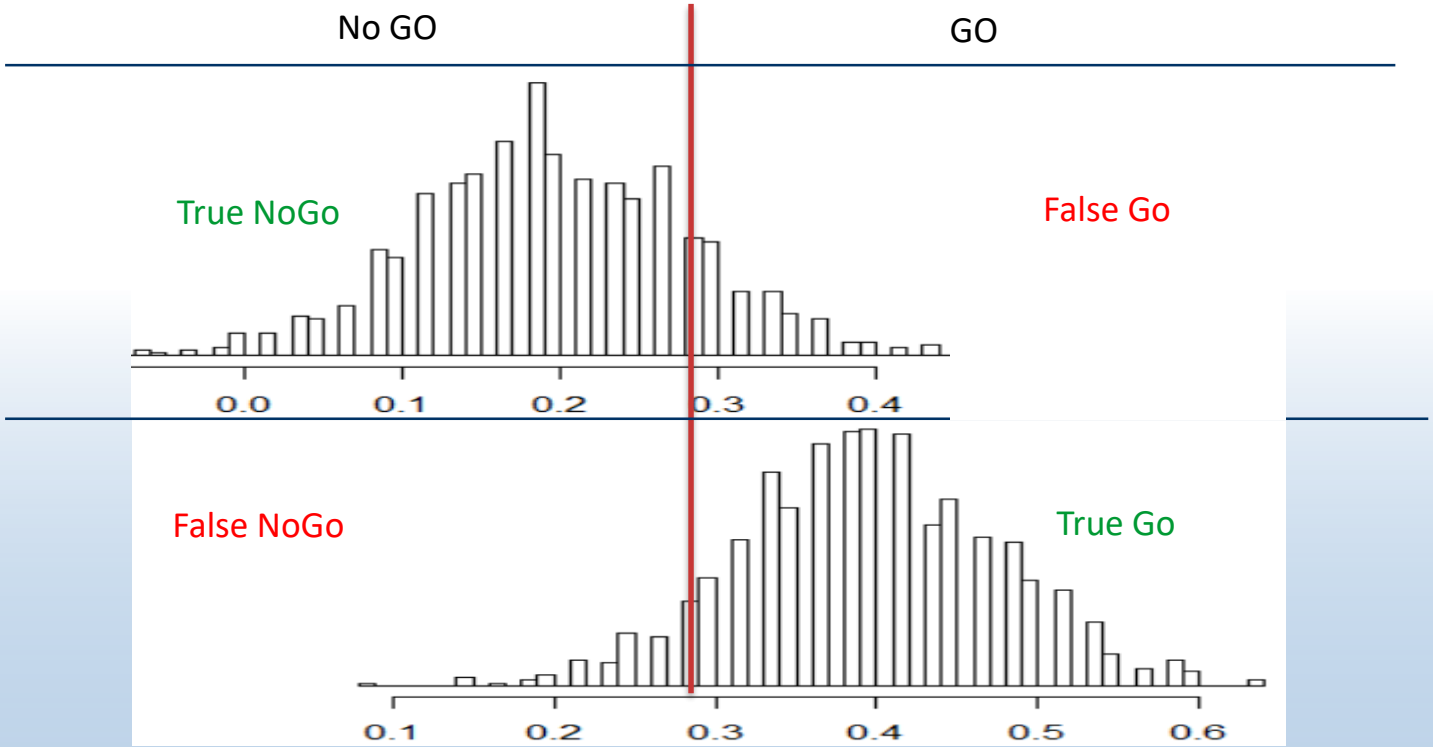


Low bar
- P(false NoGo| +) low
- P(false Go| -) high

Balance
- P(false NoGo|+) low
- P(false Go|-) low



How to quantify the risk?



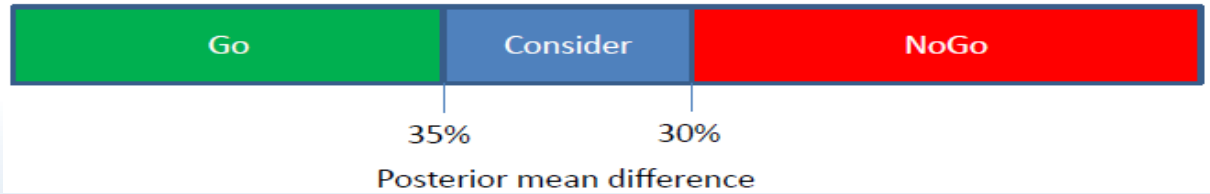
Assumptions

True effect = 0.2
non-effective

True effect = 0.4
effective

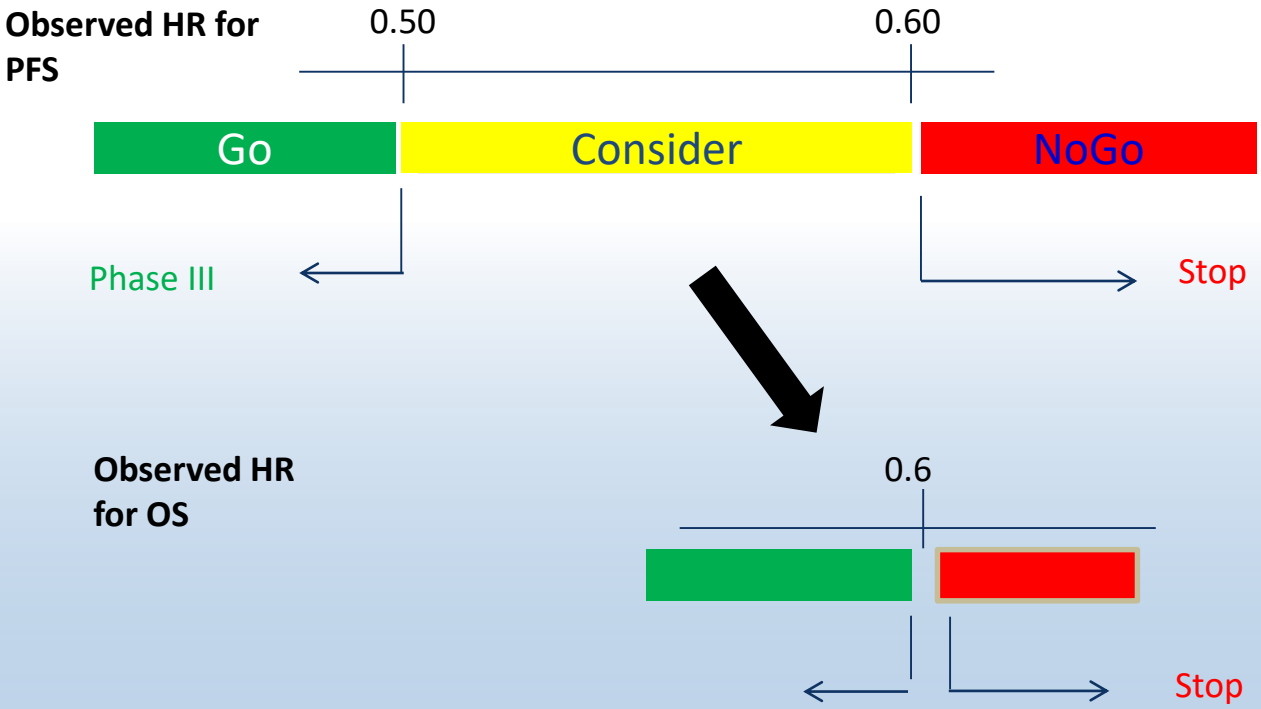
Example 1: Go/NoGo table

- Go/NoGo Based on posterior probability regarding risk difference



Case	RR Active	RR Placebo	Go Prob.	Con Prob.	NoGo Prob.
+	77%	35%	80%	15%	5%
-	55%	35%	6%	10%	84%
+ alternative	67%	25%	59%	24%	17%
- alternative	65%	45%	11%	19%	70%

Example 2: more complex decision rules



Bayesian approach

- P(effect >= 0.6 | data)
- Can augment the data by including historical control
- Various ways of borrowing historical data
  - Use historical data to form a prior
  - Static borrowing
  - Dynamic borrowing

Summary

- Predefined => increase objectivity in the decision process
- Include summary of the up-to-date evidence
- Common understanding on objectives of development/trials
- Expectation management regarding the inference obtained from a trial.
- Framework to link sample sizes directly to precision for Go / NoGo decision making
- CDP / CTP consistency
- Upfront agreement of clear recommendation regions for decision making
- Not assumption free

Go/NoGo R Shiny App

Yi-Hung Wu, Weizhi Shi

July 26, 2018

Agenda

- What is R Shiny?
- Why R Shiny?
- What is the scope of the App?
- Overview of the App

What is R Shiny?

- **R** is an open source programming language and software environment for statistical computing and graphics that is supported by the R Foundation for Statistical Computing
  - Minimalistic GUI: Command console / text editor

- **RStudio**, Inc. is a company that provides “enterprise-ready professional software” for the R environment
  - RStudio® integrated development environment (IDE) for R
    - Within RStudio® can run specific reporting / visualization packages contributed by RStudio, Inc., e.g. Shiny

- **Shiny is an extension package for interactive web applications with R**
  - No Java programming knowledge required
  - Interactive GUI
  - Free basic version available for download on CRAN

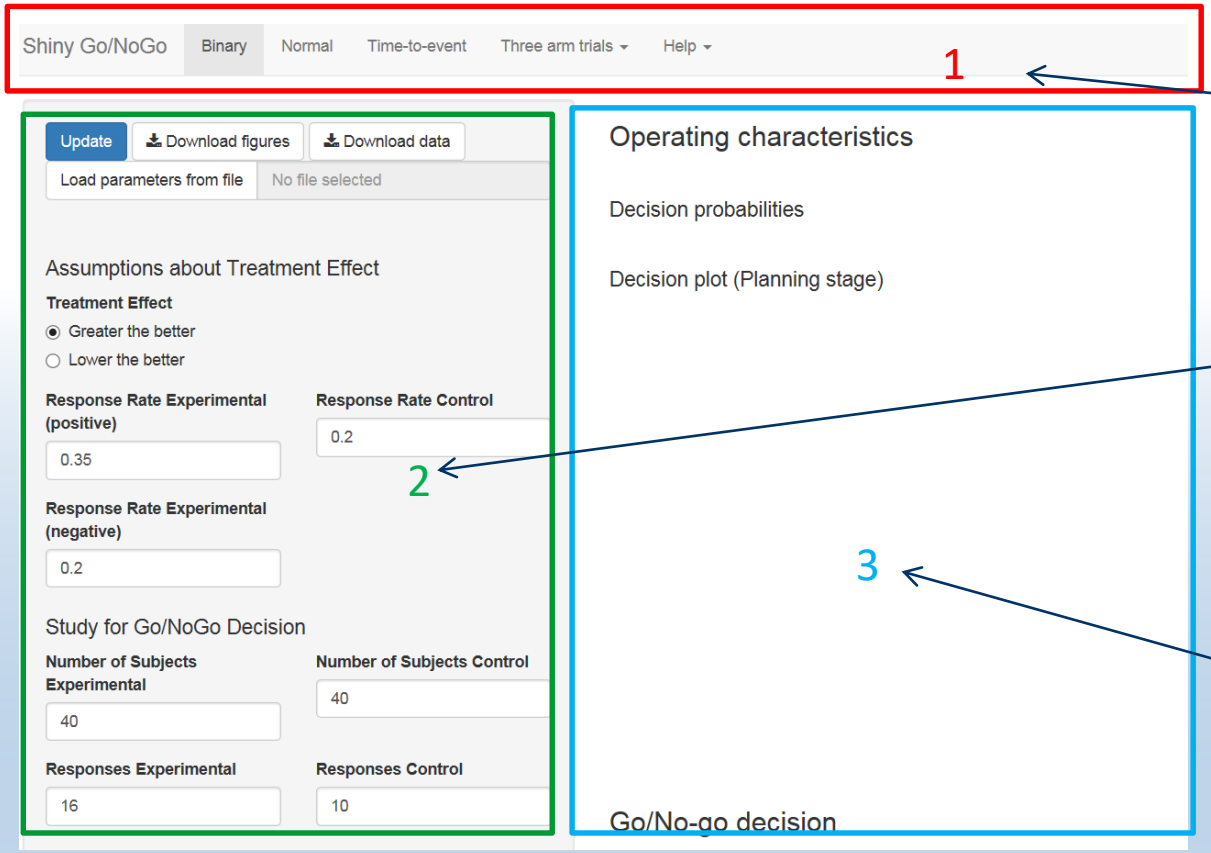
Why R Shiny?

- No readily available software/GUI for Bayesian Go/NoGo available
  - Not included in standard sample size software
  - No handy one-for-all solution including instant parameter tweaking and dynamic result rendering
- Ability to write customized code to implement desired methodology
- R Shiny well suited for this kind of interactive calculation and visualization
- Possibility to run on web-server
  - No need for user to write code in R / No need for in-depth R expertise
  - No need to run R on local desktop with limited calculating power compared to server

The scope of the App

- Implementation of Bayesian Go/NoGo
  - Support latest methodological initiative
  - Interactively compute and visualize
    - Decision probabilities at trial planning stage
    - Go/NoGo decision at analysis stage
  - Implement 3 basic data types
    - Binary data
    - Normal data
    - Time to evet data
- Supporting Project Statisticians and Project Teams to evaluate Go/NoGo decisions for early clinical development such as PoCP (Proof of Clinical Principle)

General overview

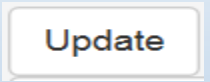


1. Navigation bar

Choose data type (binary, normal, TTE) or access help resources (manual)

2. User input panel

Input user specs
Start/update calculation

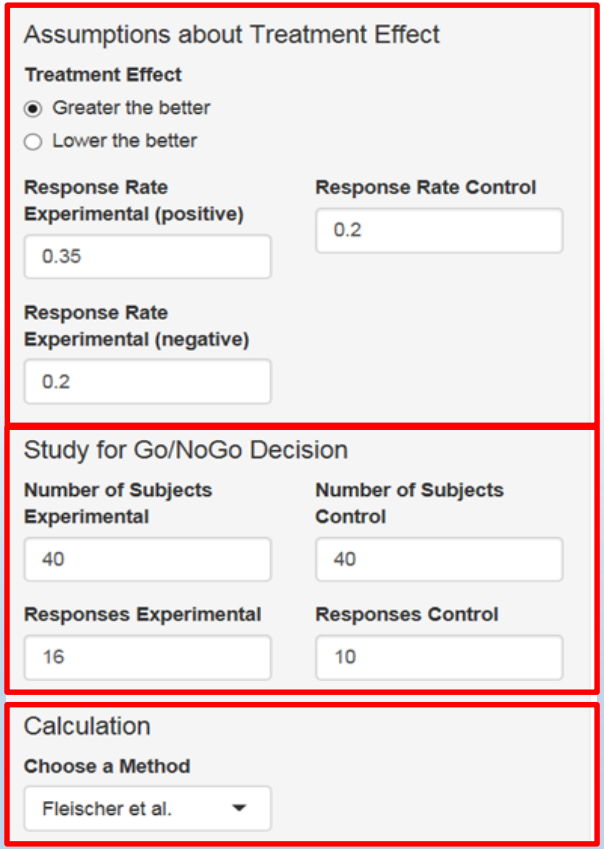


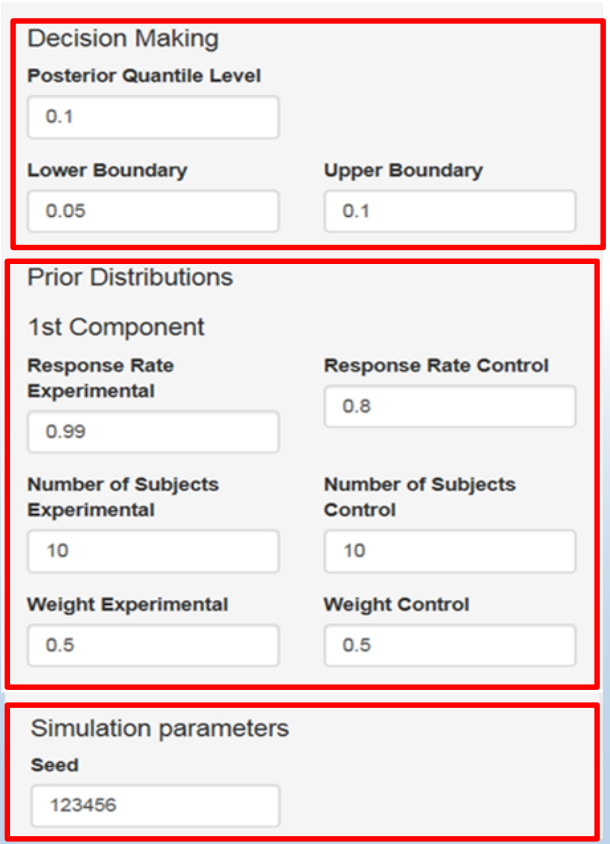
Download inputs/results/ /logs

3. Output panel

View results (after update)

Specification of a binary data design





Output

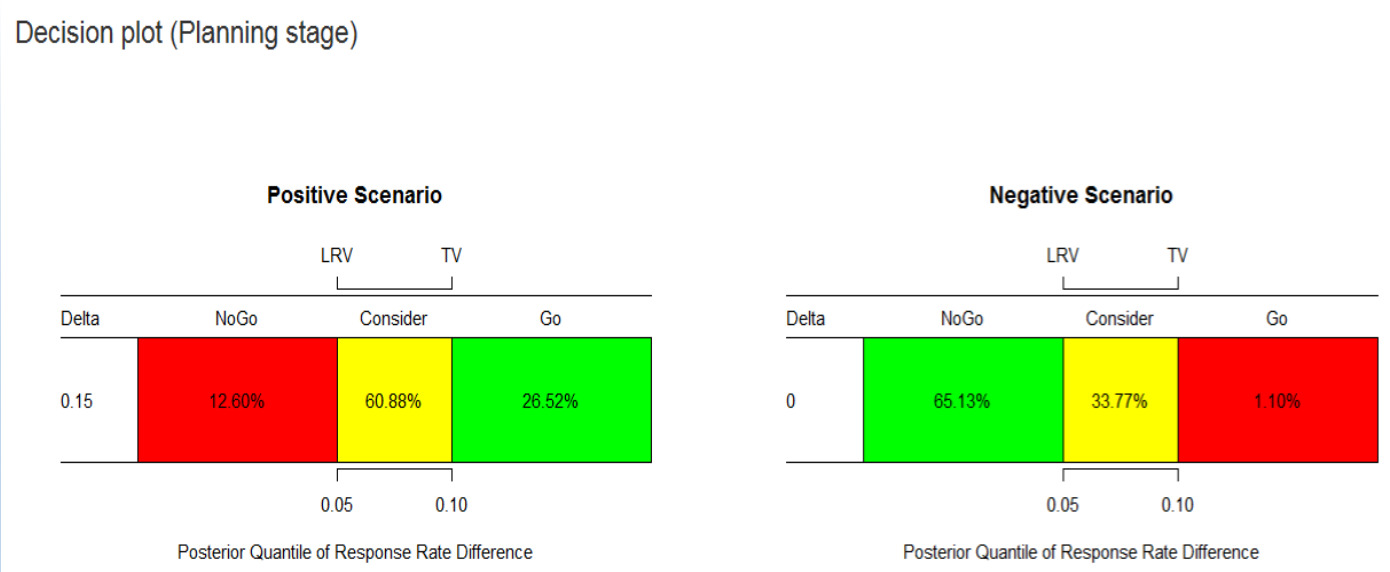
- Output follows the same layout for all data types
  - Decision probabilities in positive/negative scenario
  - Actual decision for given data
  - Density plots for given data

Operating characteristics of a binary data design

Decision probabilities

Scenario	Prob. for NoGo	Prob. for Consider	Prob. for Go
Positive	12.60%	60.88%	26.52%
Negative	65.13%	33.77%	1.10%

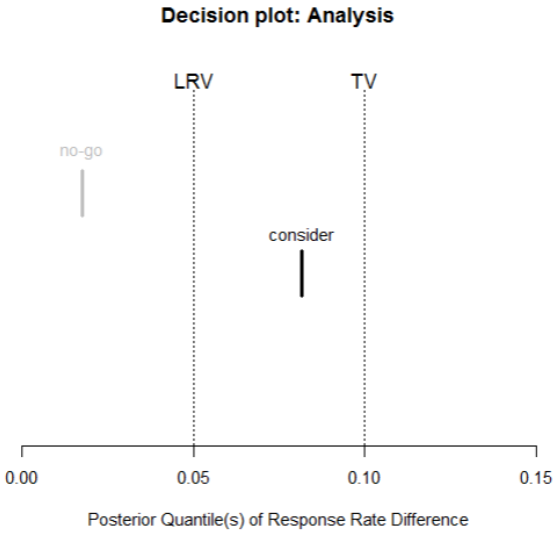
Decision plot (Planning stage)



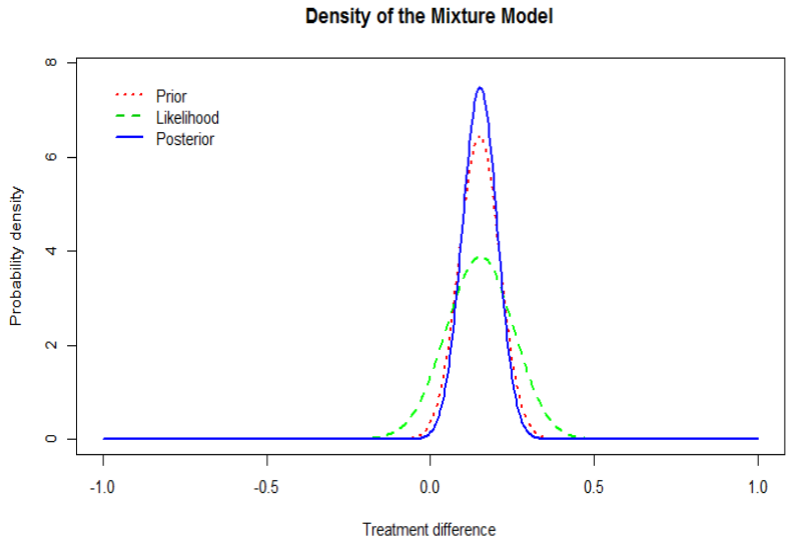
Decision and Density plot for given data in a binary data design

Go/No-go decision

Decision plot (Analysis stage)



Density plot



Questions?

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