AstraZeneca

Multiple Endpoints in Early Phase Decision Making

Aleksandra Buchowicz

Chris Gibbs

Agenda

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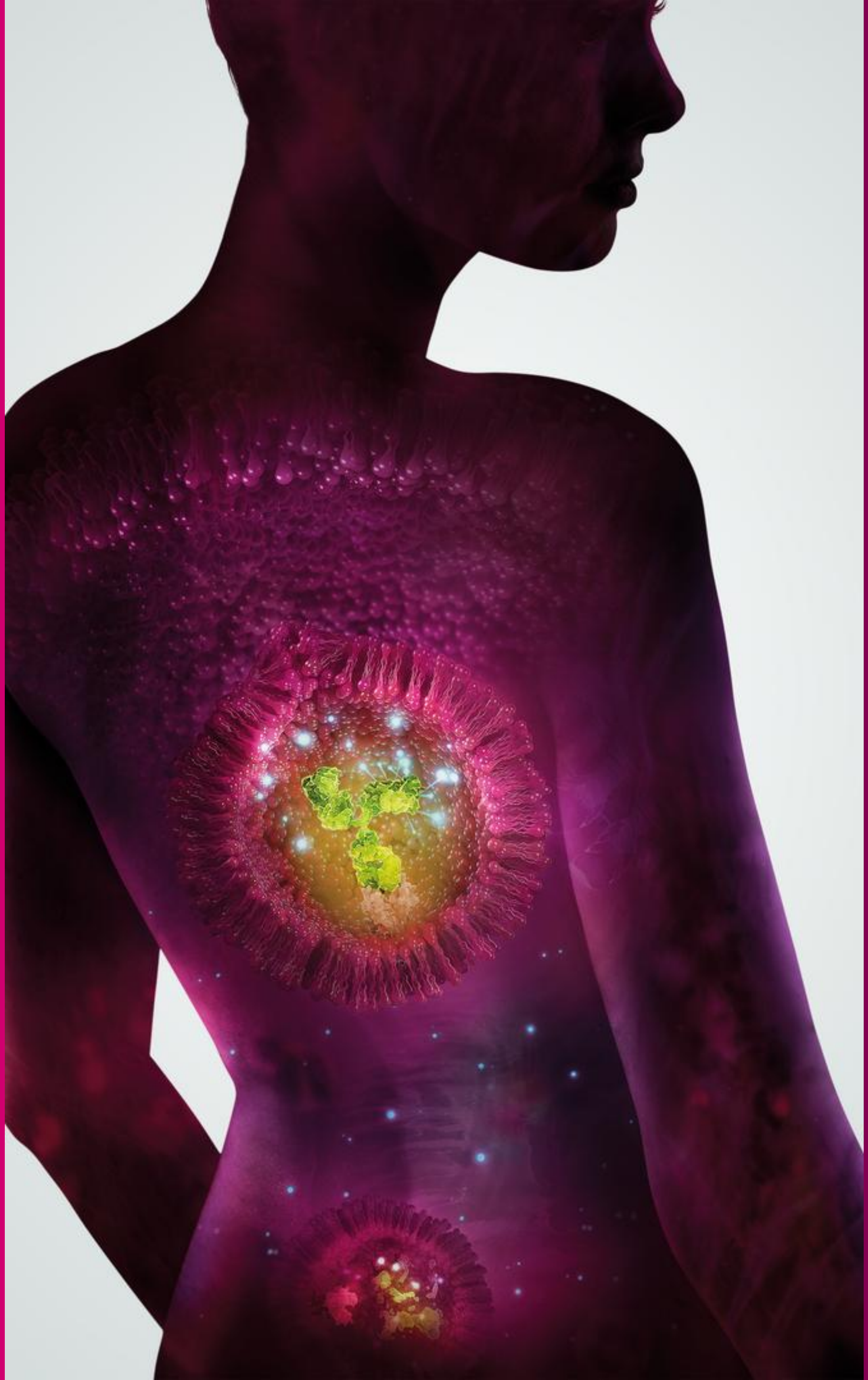
2. Independent endpoints
3. Correlated data
4. Implementation
5. Q&A



Introduction

Standard decision framework at AstraZeneca

Decision making in Early Phase Oncology

- Candidate-rich early phase portfolio
- We want to prevent exposing patients to ineffective and toxic therapies
- It is also essential to avoid wasting time and resources on unpromising drugs
- Need for clear & quick decision making

Decision points in Early Clinical Trial Development

Three-outcome decision framework

Go

Evidence to proceed with development of drug

Consider

Evaluate the totality of evidence to decide on next steps or gather more evidence

Stop

Lack of evidence to continue development of drug

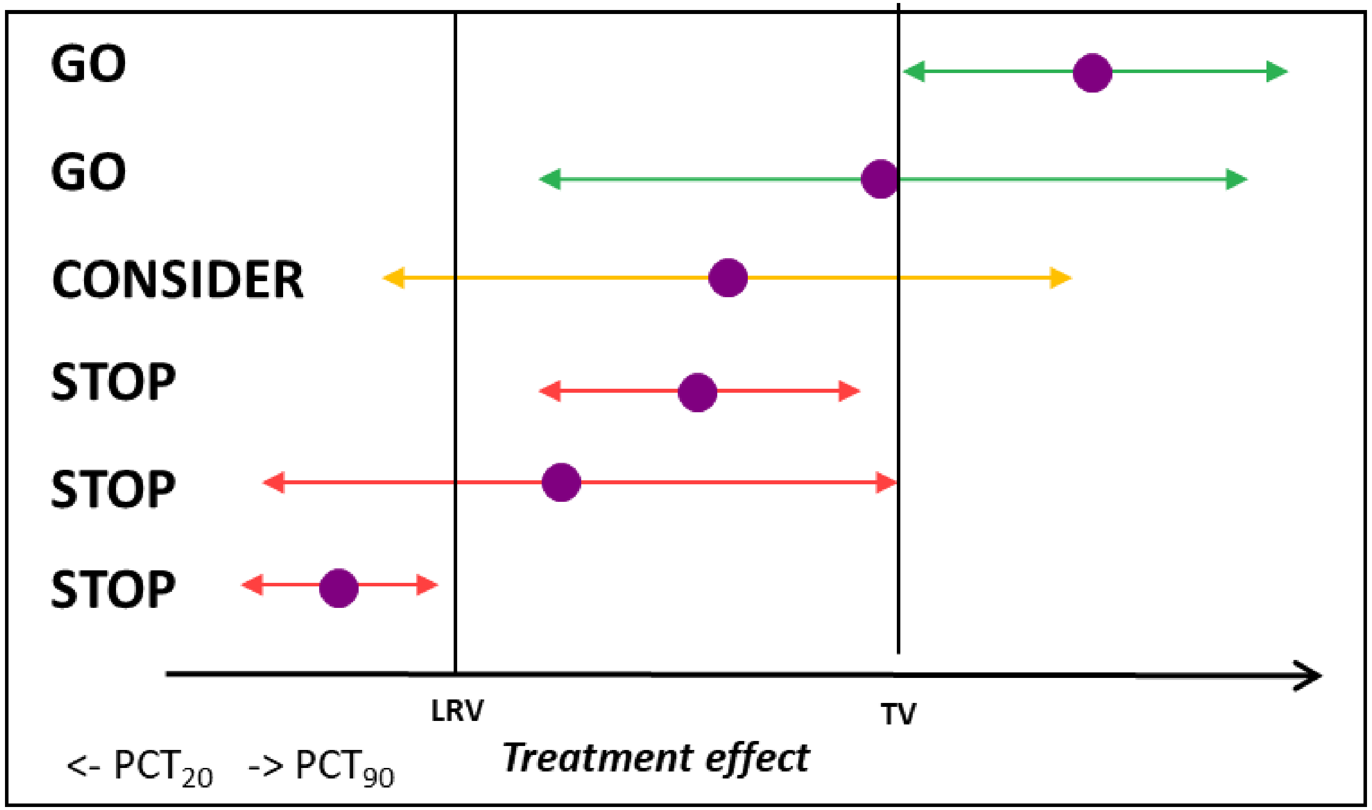
Decision parameters

Target value (TV)	Desired level of performance
Lower Reference Value (LRV)	Minimally clinically significant level of performance
False Stop risk	Risk of stop decision when TV or better is true (typically 10%)
False Go risk	Risk of go decision when LRV or worse is true (typically 20%)

- The LRV and TV need to be **evidence based** and **scientifically justified**
- This method uses the upper and lower confidence intervals of a treatment effect

Visualization of Decision Framework

Point estimates & corresponding CI



Decision criteria

Go if (green): PCT_{20} > LRV and PCT_{90} > TV

Consider if (amber): $PCT_{20} \leq$ LRV and PCT_{90} > TV

Stop if (red): $PCT_{90} \leq$ TV

***PCTx denotes the xth percentile of the distribution of the treatment effect**

Decision making with multiple endpoints

- Many trials evaluate multiple endpoints, typically estimating operating characteristics separately
- When two endpoints are used, overall decisions based on the outcome of each endpoint can be formulated as a 3x3 matrix of each endpoint result
- Joint operating characteristics should be estimated to achieve a better representation of the overall decision making
  - Viewing each endpoint separately may lead to misleading operating characteristics

Example of an overall decision matrix

		Endpoint 2 Go/NoGo		
		Go	Consider	Stop
Endpoint 1 Go/NoGo	Go	Go	Go	Consider
	Consider	Go	Consider	Stop
	Stop	Consider	Stop	Stop

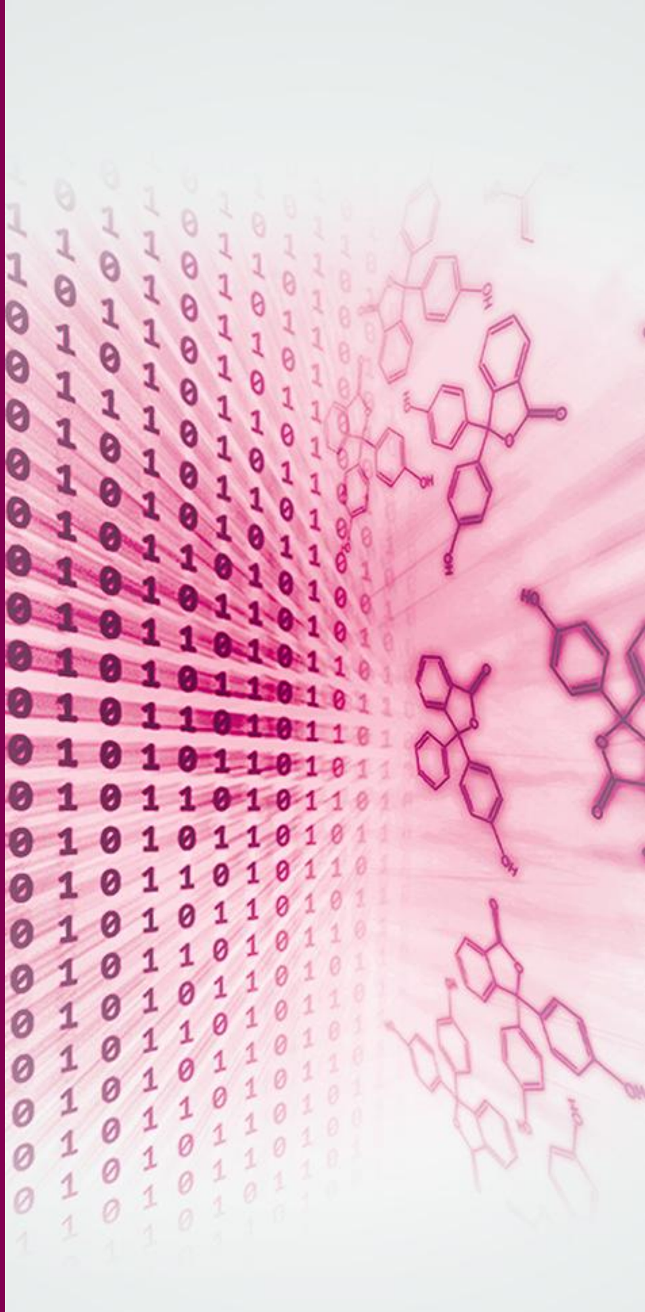
Scope and limitations

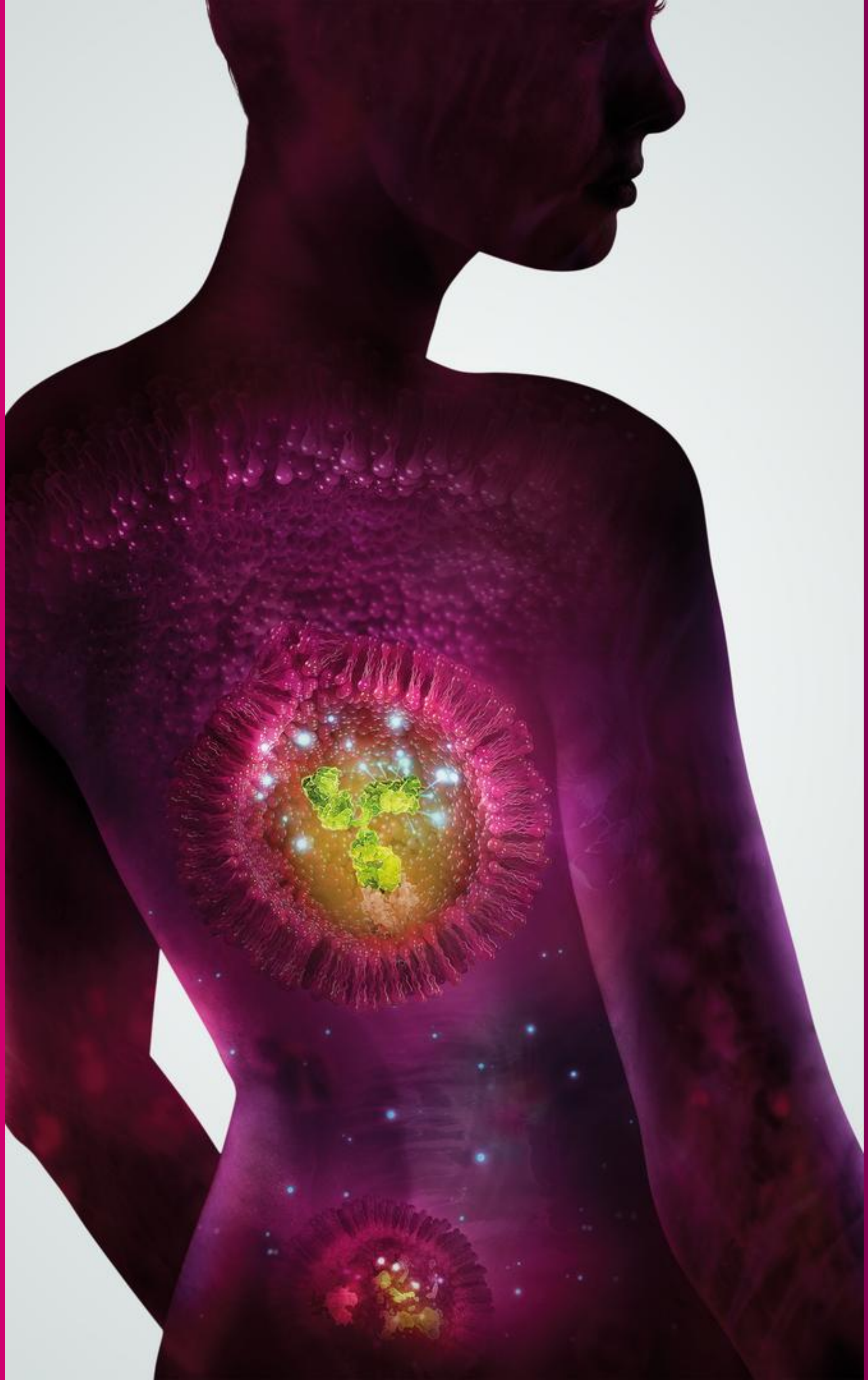
In scope

- Method implemented for 2 endpoints only
- Focus on oncology endpoints (binary & TTE)
- Pearson correlation only
- Operating characteristics using precalculated go/stop cutoffs

Out of (initial) scope

- Estimating the correlation between endpoints
- Calculating cutoffs on correlated data





Independent endpoints

Assuming independence – Joint decision matrix

Endpoint 1		**Endpoint 2**	
TV	LRV	TV	LRV
Go	Go	Go	Go
Consider	Consider	Consider	Consider
Stop	Stop	Stop	Stop

		Endpoint 2		
		Go	Consider	Stop
Endpoint 1	Go			
	Consider			
	Stop			

Joint decision matrix.

Which boxes are ultimately Go/Consider/Stop shall be determined by the study team, and our tool gives the flexibility to change this

Constructing Joint Operating characteristics

Example: Both endpoints under TV

Endpoint 1 = TV

0.76	Go
0.14	Consider
0.10	Stop

Endpoint 2 = TV

0.85	Go
0.06	Consider
0.08	Stop

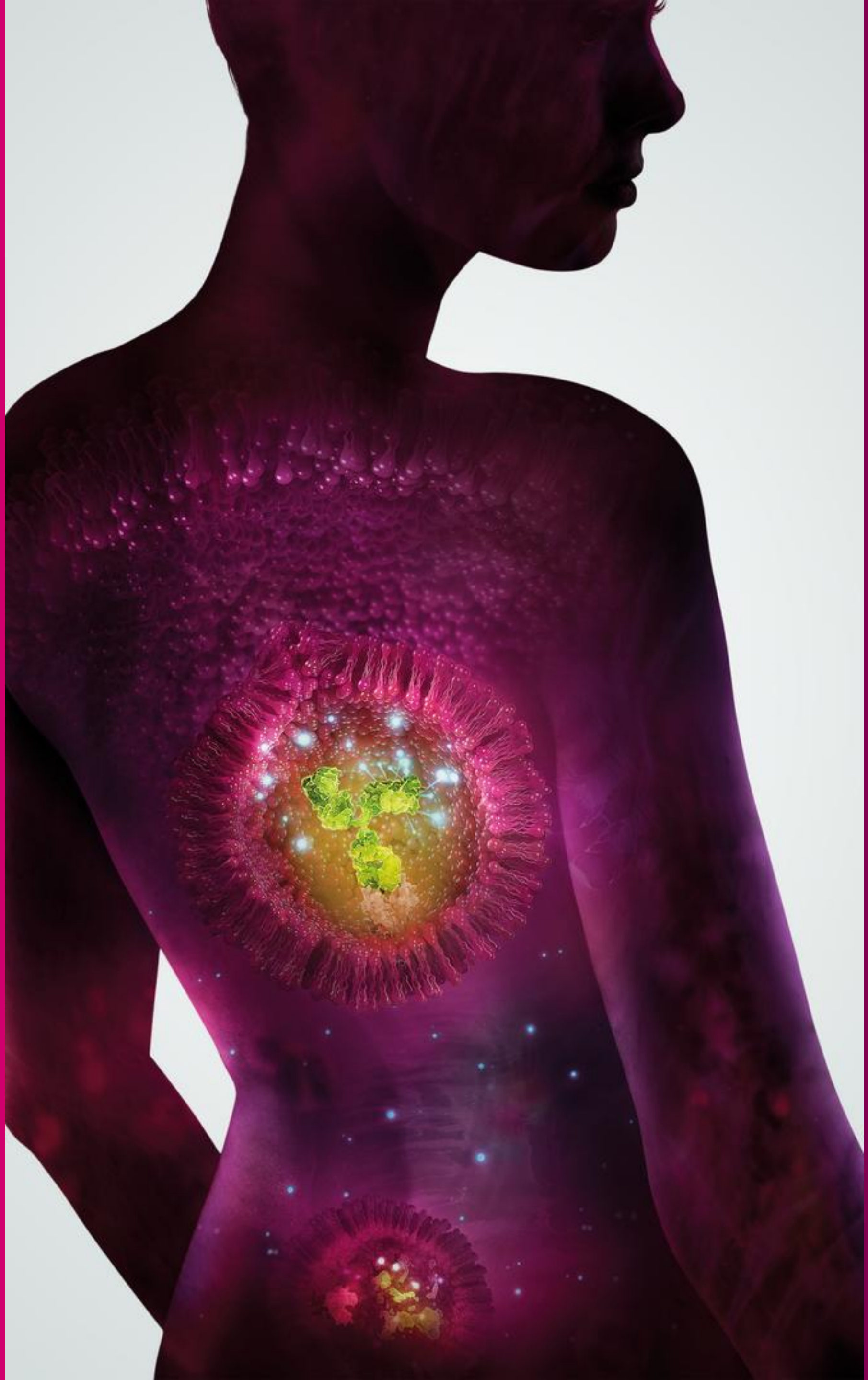
		Endpoint 2		
		Go	Consider	Stop
Endpoint 1	Go	0.76 x 0.85 = 0.65	0.76 x 0.6 = 0.05	
	Consider	0.14 x 0.85 = 0.12		
	Stop			

Sum of "Go" in the matrix = 0.65 + 0.12 + 0.05 = 0.82

Assuming independence – Constructing Joint Operating characteristics

		Endpoint 2		
		Go	Consider	Stop
Endpoint 1	Go	0.65 (0.76 x 0.85)	0.05	0.06
	Consider	0.12	0.01	0.01
	Stop	0.09	0.01	0.01

Sum of "Go" in the matrix = 0.65 + 0.12 + 0.05 =	0.82
Sum of "Consider" = 0.09 + 0.01 + 0.06 =	0.16
Sum of "Stop" = 0.01 + 0.01 + 0.01 =	0.03



Correlated data

Correlated endpoints

BE1

Operating characteristics are straightforward to calculate under the independence assumption. However, in most cases there likely is correlation between the endpoints.

For example, if endpoints have high positive correlation, in some scenarios ***independent modelling may underestimate the false positive rate.***

How to handle correlated data? We took a ***simulation-based approach***.

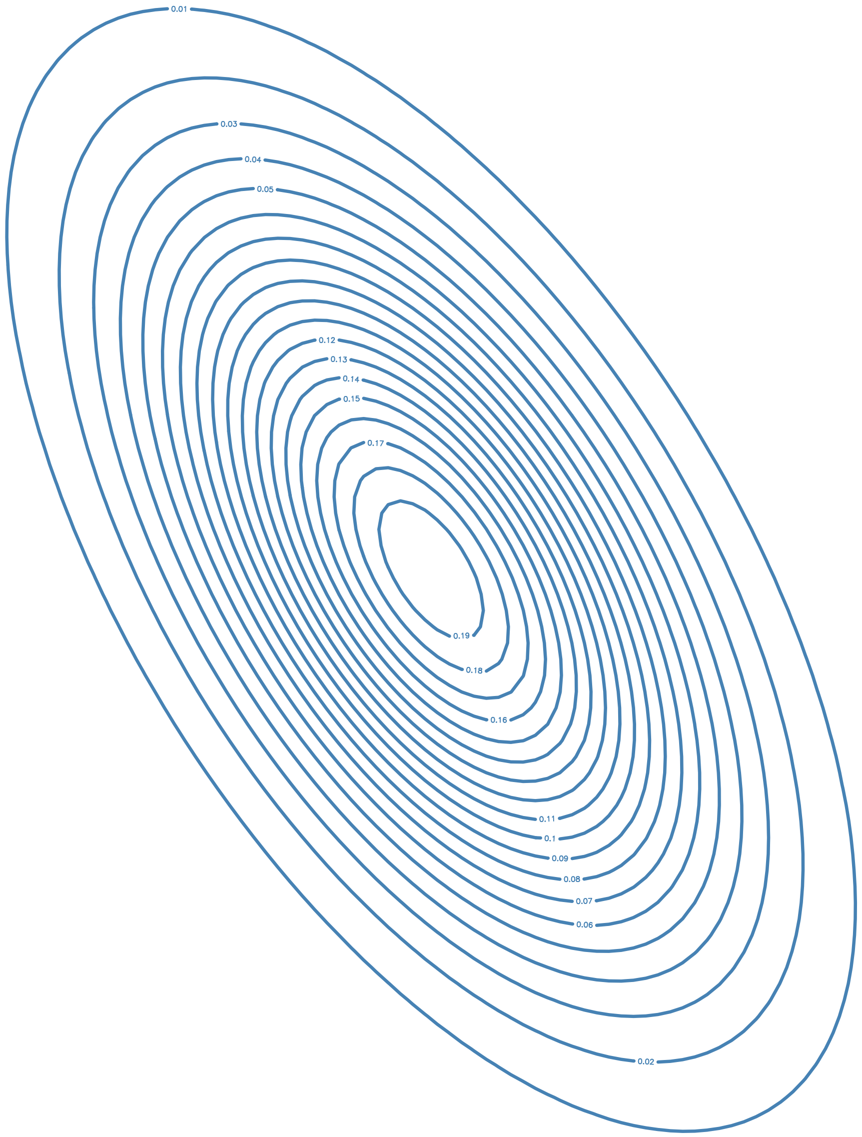
BE1

Method overview

Simulate from marginal distributions independently

Construct a joint distribution through an iterative reordering method while retaining original marginal distributions

Utilize the established GNG cut-offs and joint decision matrix to calculate operating characteristics



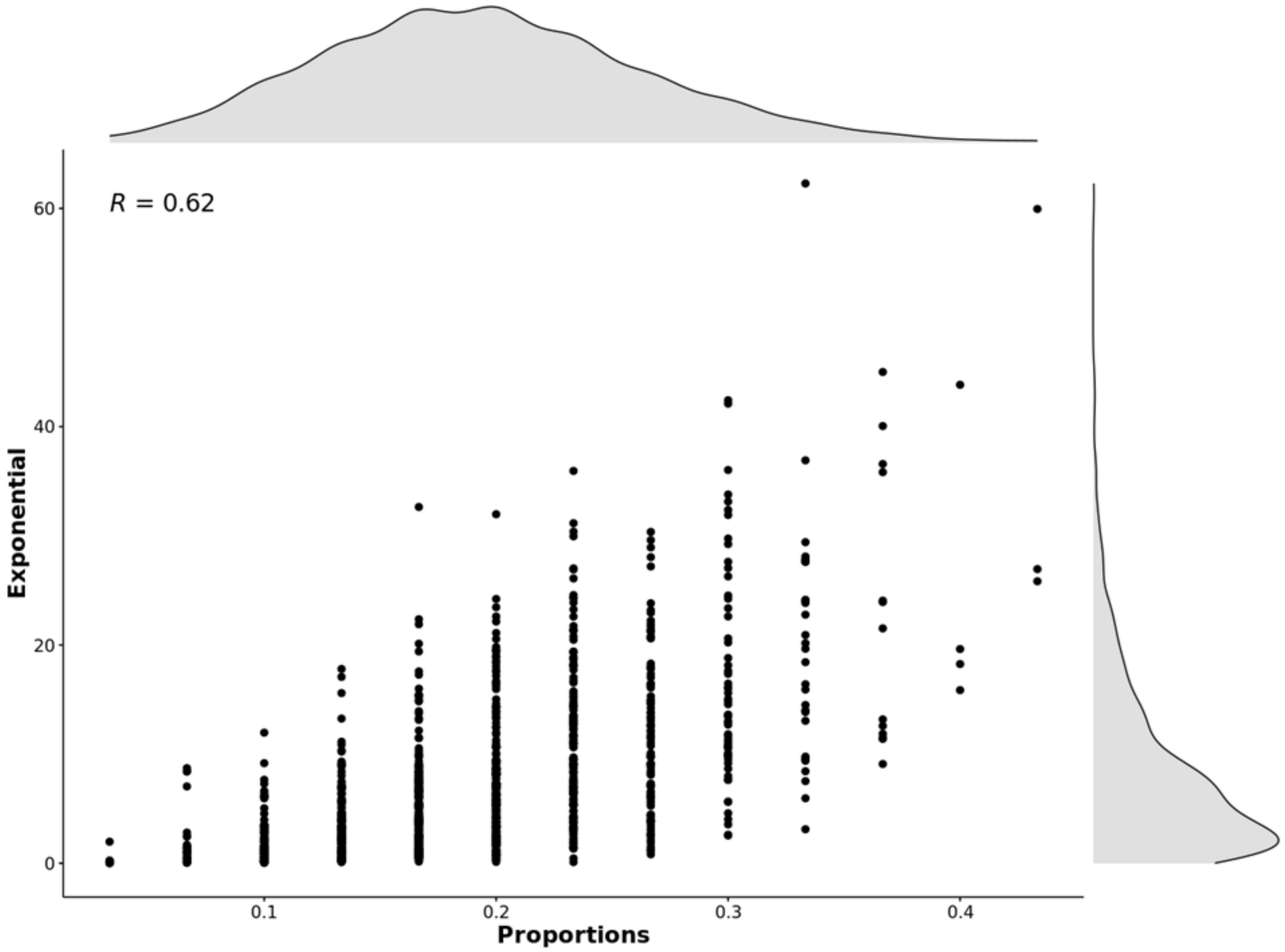
A word on gaussian copulas

Multivariate normal data with desired correlation → Uniform distribution using normal CDFs → Desired marginal distribution using inverse CDFs

However:

- Pearson correlation is not always preserved through transformations of the margins e.g. for binomial distribution.
- Additional considerations are needed when constructing non-normal marginals and Pearson correlation.

Pearson correlation not preserved



- The targeted Pearson correlation coefficient is not preserved when marginals are non-normal due to non-linear transformations from the joint distribution to the marginal
- An example of this:
  - Target Pearson correlation = 0.7
  - Binomial and exponential marginals
  - Observed correlation = 0.62
- Need to adjust target correlation to reach the desired observed correlation and may reach an upper limit at higher correlations

Ruscio-Kaczetow iteration: introduction

A bit of mathematics

- Let Σ be an K x K positive semi-definite correlation matrix
- Let S be an N x K noise matrix with uncorrelated columns of equal variance

Then, **for any decomposition of the form $\Sigma = U^T U$ the correlation matrix of Y = SU is Σ**.

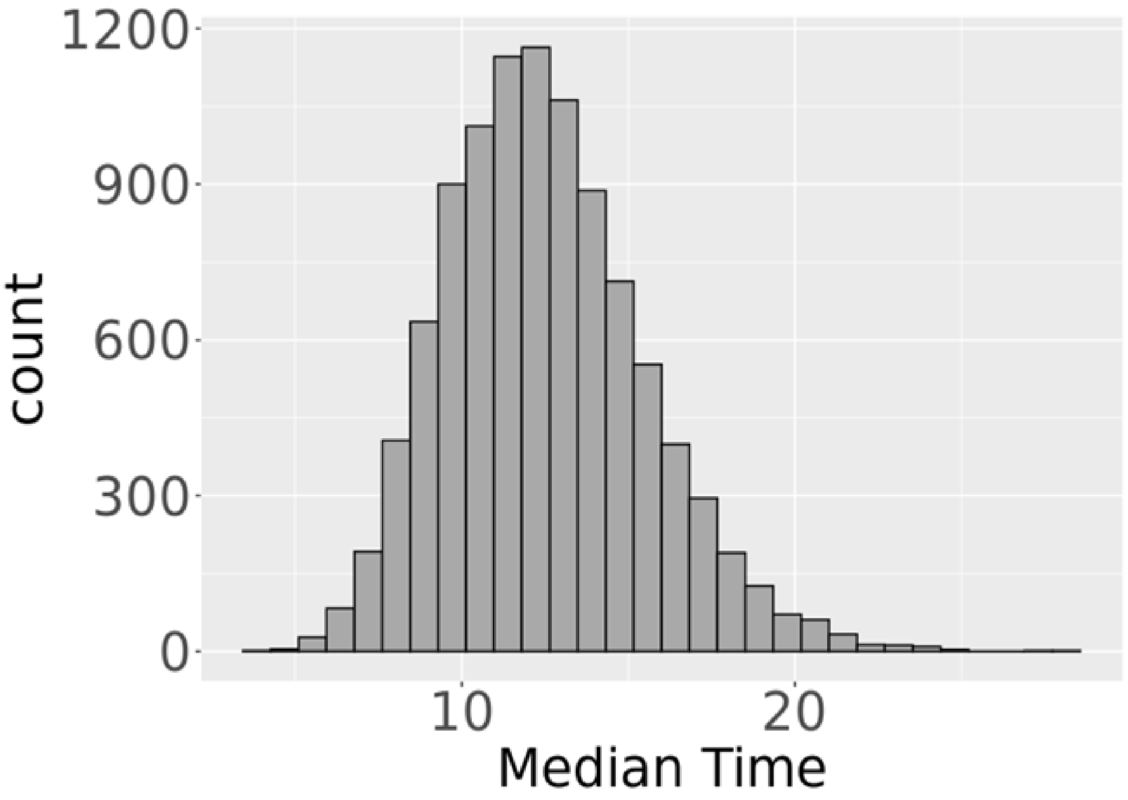
This includes the Cholesky and eigenvalue decompositions.

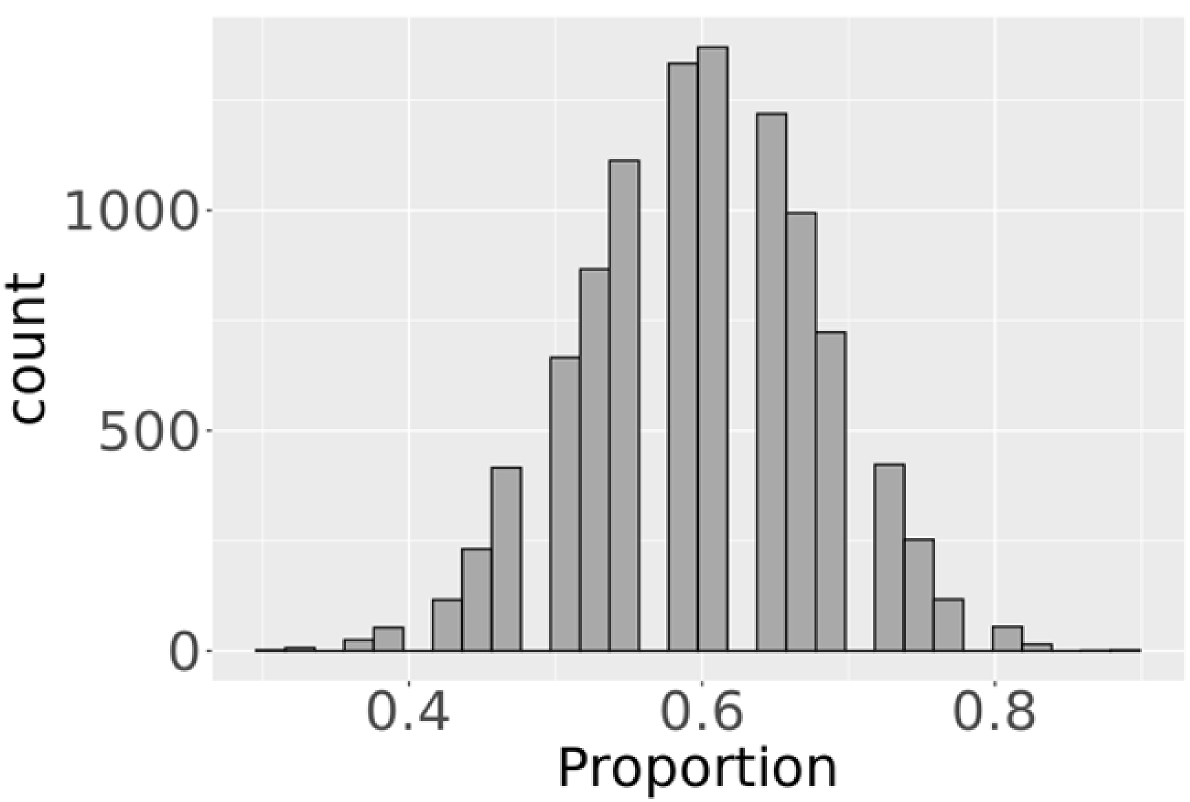
Ruscio-Kaczetow iteration for joint distribution

1. Given two marginals (X_1,X_2) of any distribution and a target Pearson correlation (Σ_{target}), produce Corr(X_1,X_2)$\approx\Sigma_{target}$
   - Keep marginal values, only change their order to introduce dependence
2. Start with a matrix of uncorrelated marginals, S= [X_1,X_2]
3. Factorize target Pearson correlation, $\Sigma_{target}=A^TA$
4. Compute a new matrix Y = SA, so Corr(Y) $\approx \Sigma_{target}$
5. Re-order elements of X_1,X_2 to the rank order of Y
6. Compute $\Sigma_{reached}$ = Corr(re-ordered X_1,X_2) and residual $\Delta = \Sigma_{target} - \Sigma_{reached}$
7. Use the error to adjust new target matrix Σ_{target}
8. Repeat until error converges

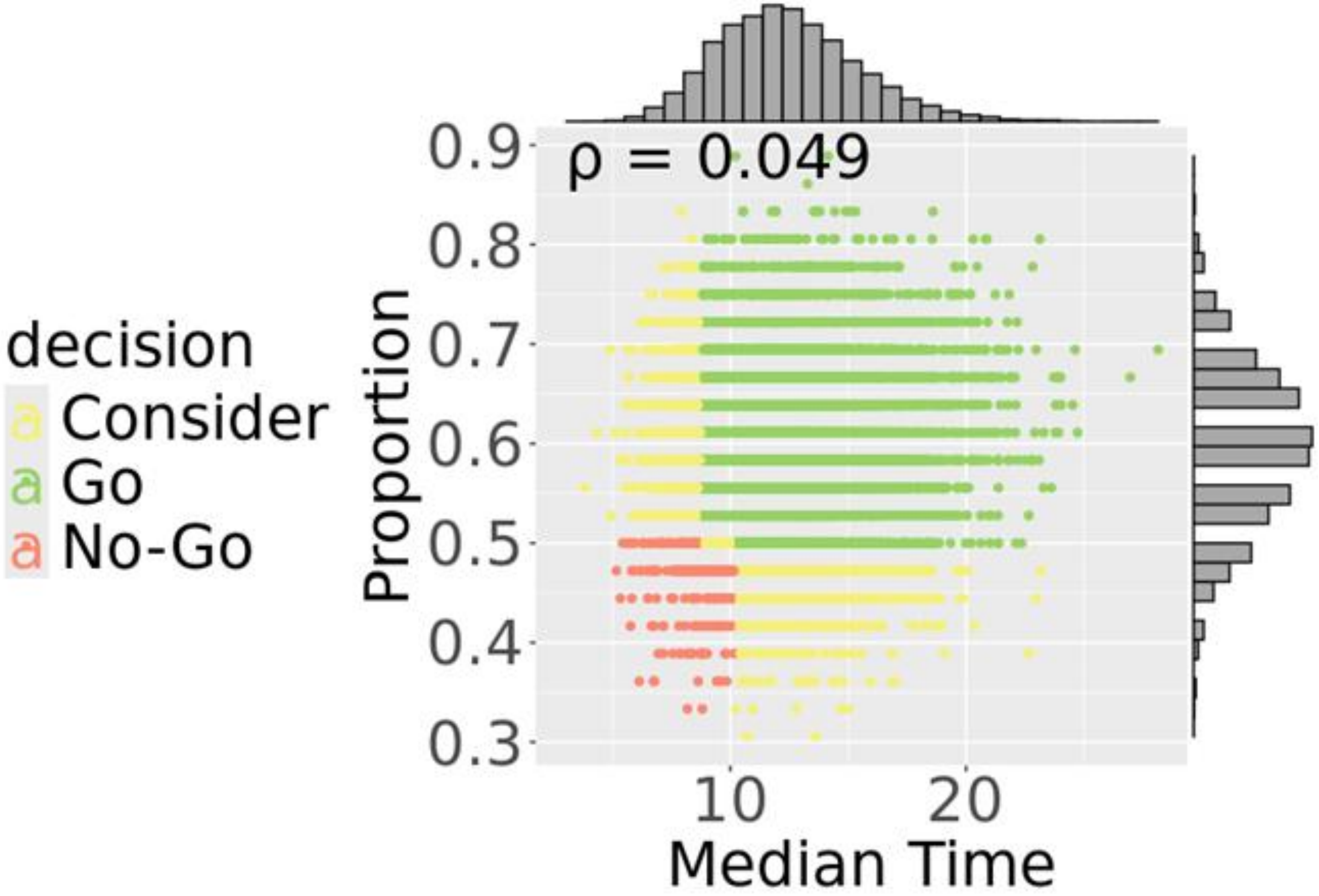
Example

1. Simulate endpoints independently: mTTE and binomial

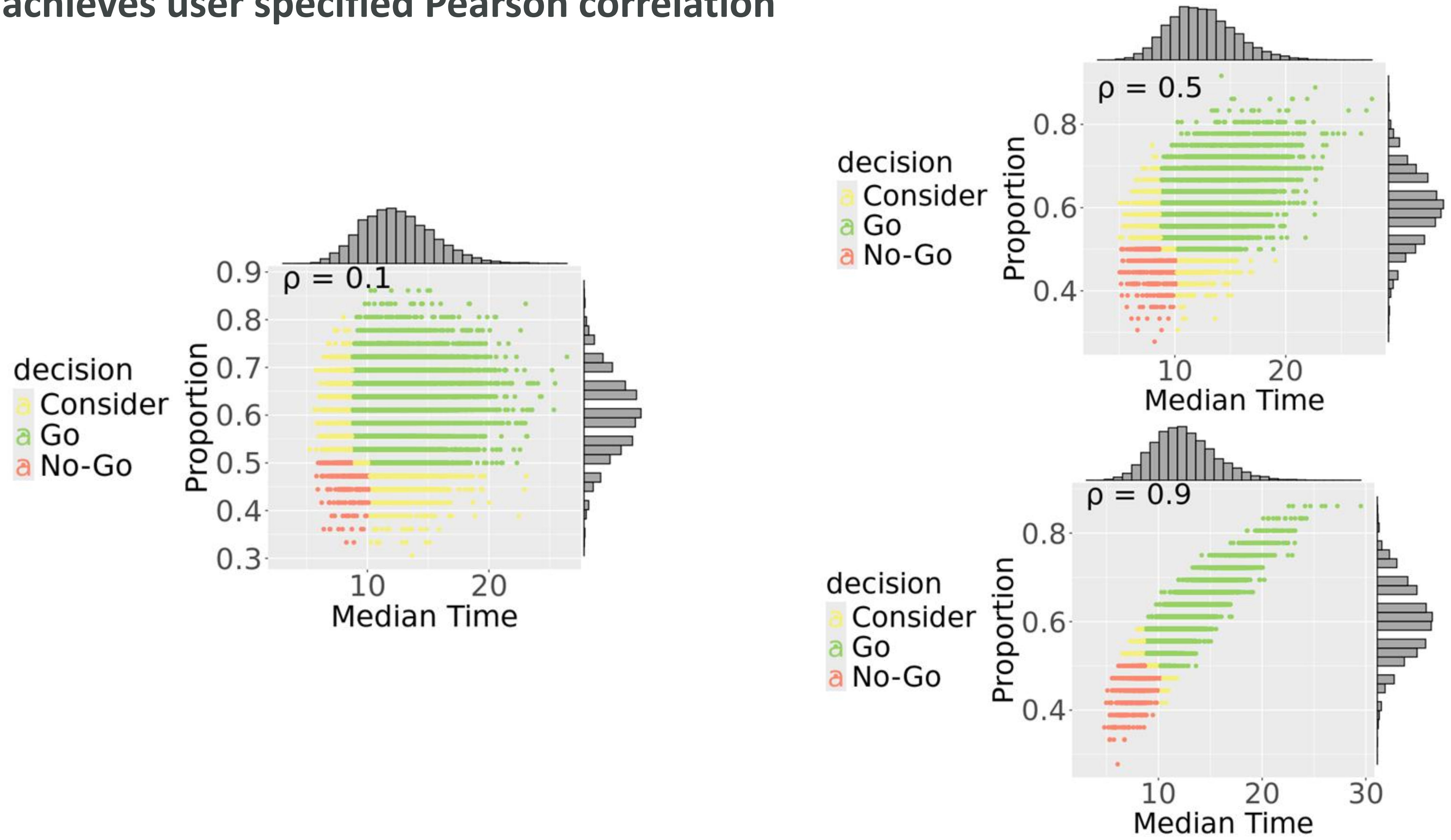


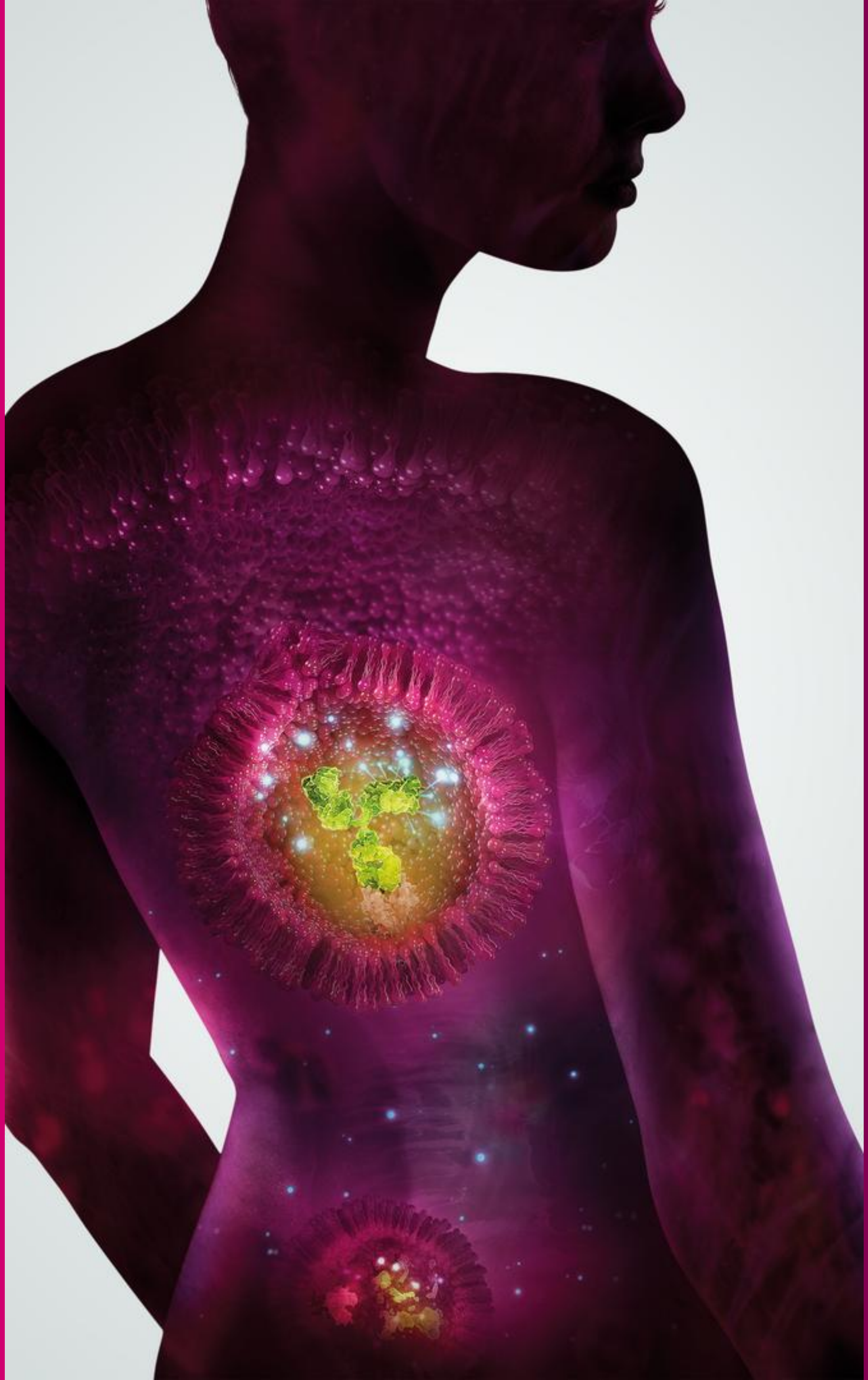


2. Combine to create joint distribution that is uncorrelated while maintaining marginal distributions



3. Apply Ruscio-Kaczetow iteration transformation to generate joint distribution that achieves user specified Pearson correlation





Implementation

Example: combining ORR and mPFS

Parameter	Endpoint 1: ORR	Endpoint 2: mPFS
Type	Binomial	Median time-to-event
TV	60%	12.3
LRV	40%	8.3
Go cutoff	53%	10.17
No-go cutoff	47%	8.76

Decision matrix

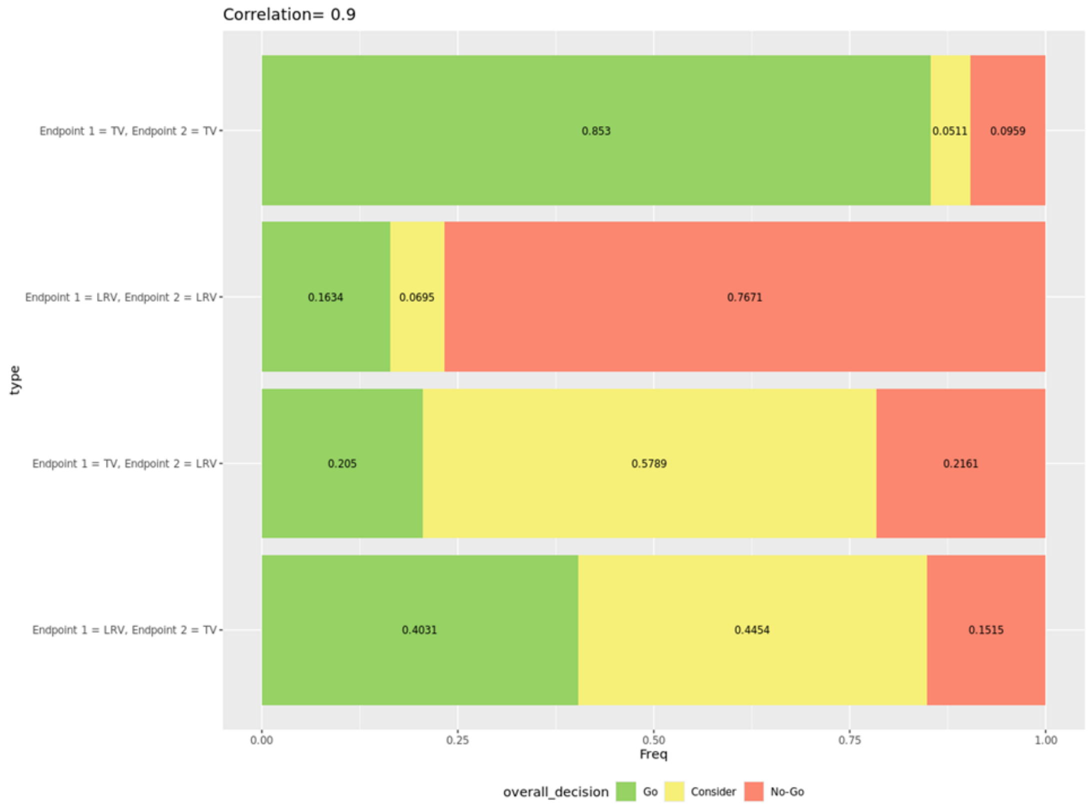
Overall GNG				
ORR		mPFS		
		Go	Consider	Stop
		mPFS ≥ 10.17	mPFS6 > 8.76 and < 10.17	mPFS ≤ 8.76
Go	ORR ≥ 53%	Go	Go	Consider
Consider	ORR > 47% and < 53%	Go	Consider	Stop
Stop	ORR ≤ 47%	Consider	Stop	Stop

Action for each Overall GNG Criteria	
Overall GNG	**Action**
Go	Start Phase III Study
Consider	Investigate DoR
Stop	Stop Development

Operating characteristics (correlation = 0.9)

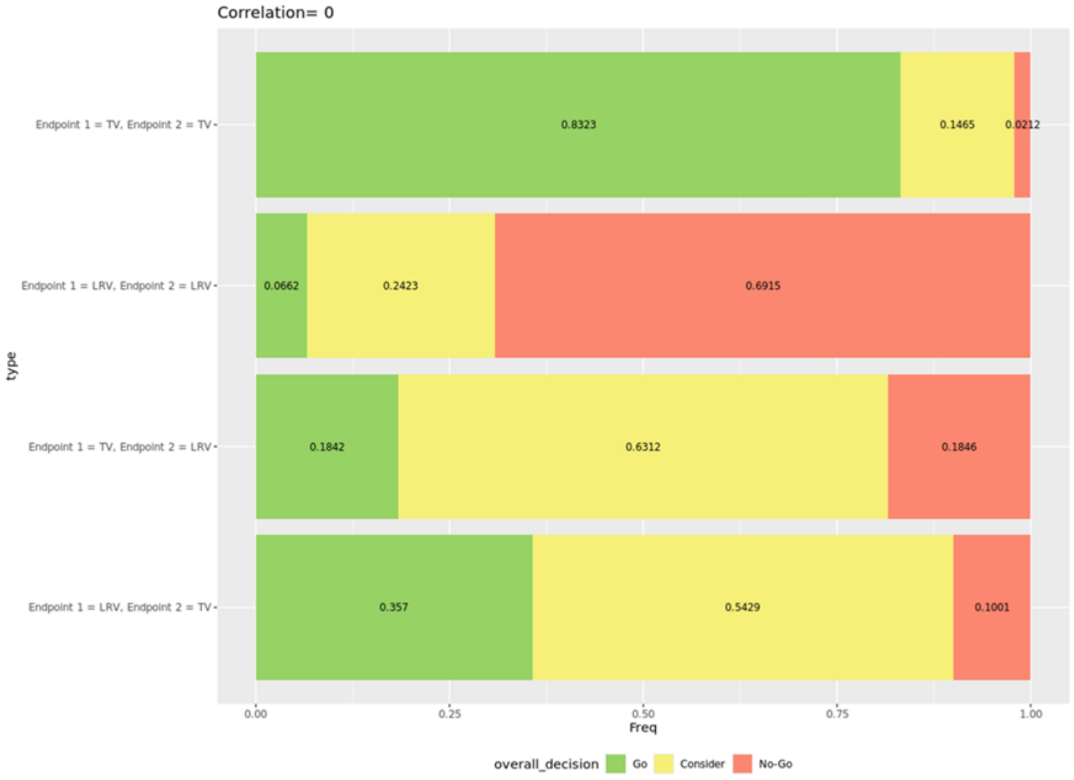
Joint Operating Characteristics

	ORR			
	TV		LRV	
	mPFS		mPFS	
	TV	LRV	TV	LRV
Go	85.30%	40.30%	20.50%	16.30%
Consider	5.10%	44.50%	57.90%	7.00%
Stop	9.60%	15.20%	21.60%	76.70%

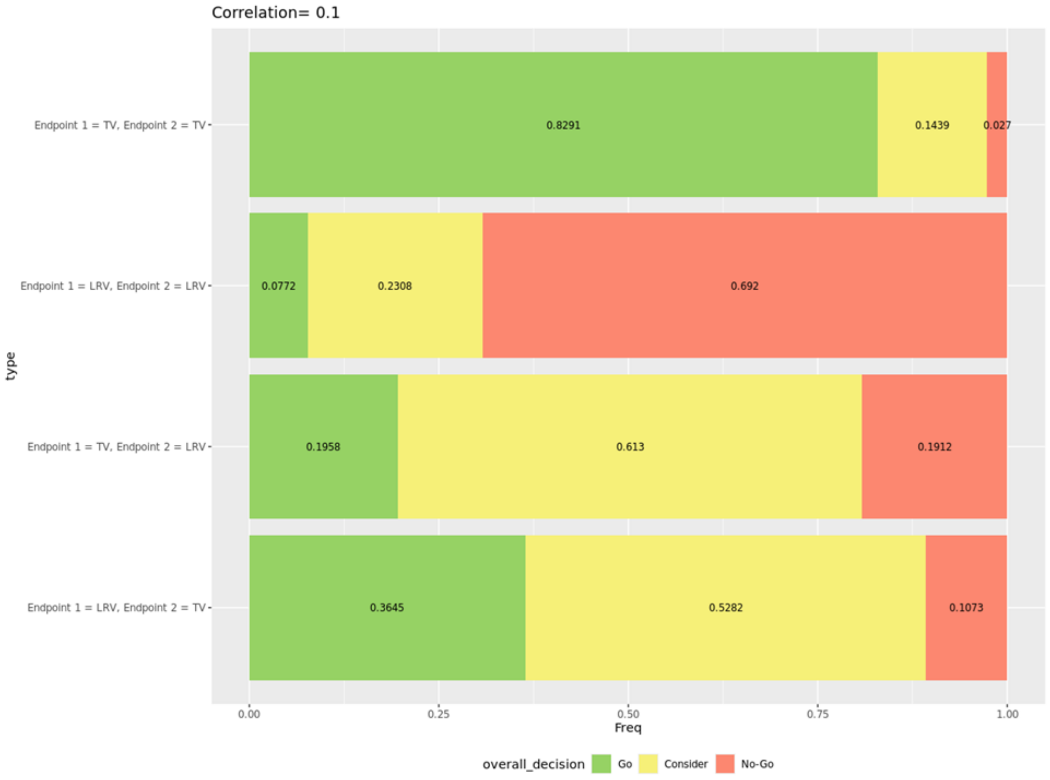


Impact of correlation

Correlation = 0.0

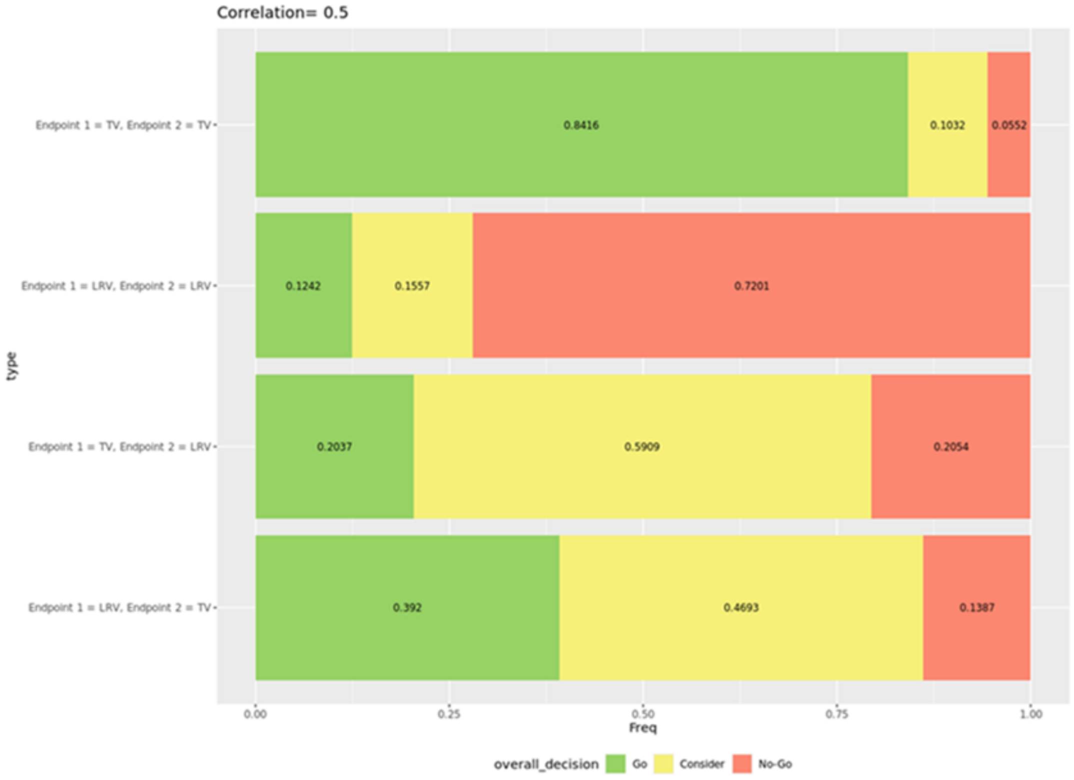


Correlation = 0.1

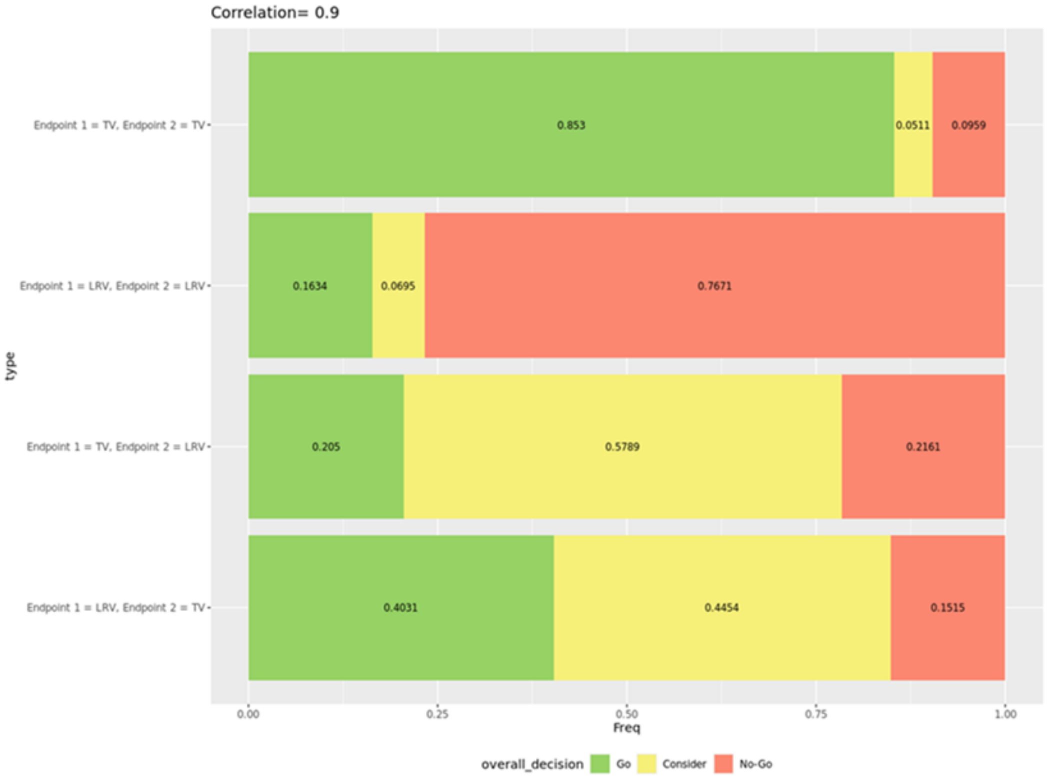


Impact of correlation

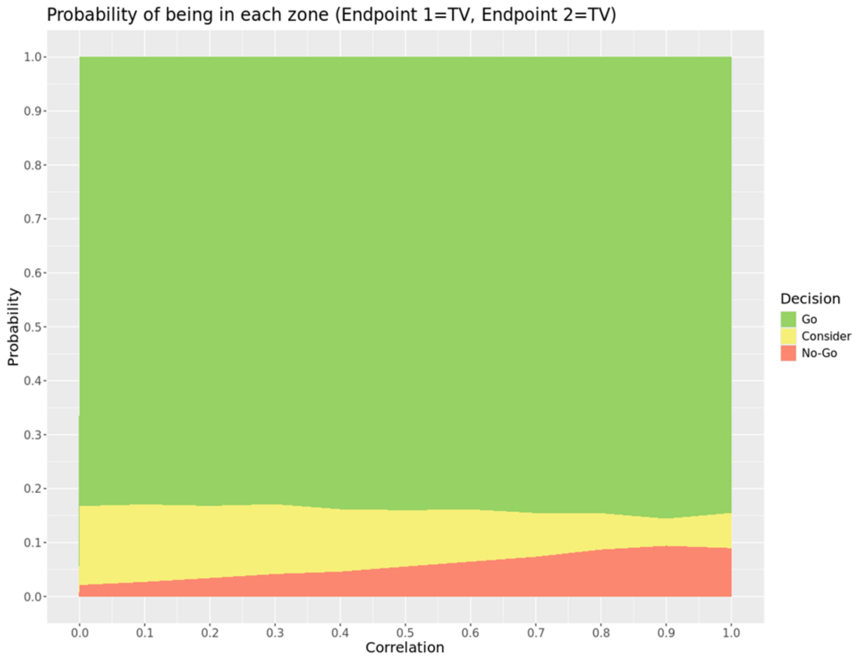
Correlation = 0.5

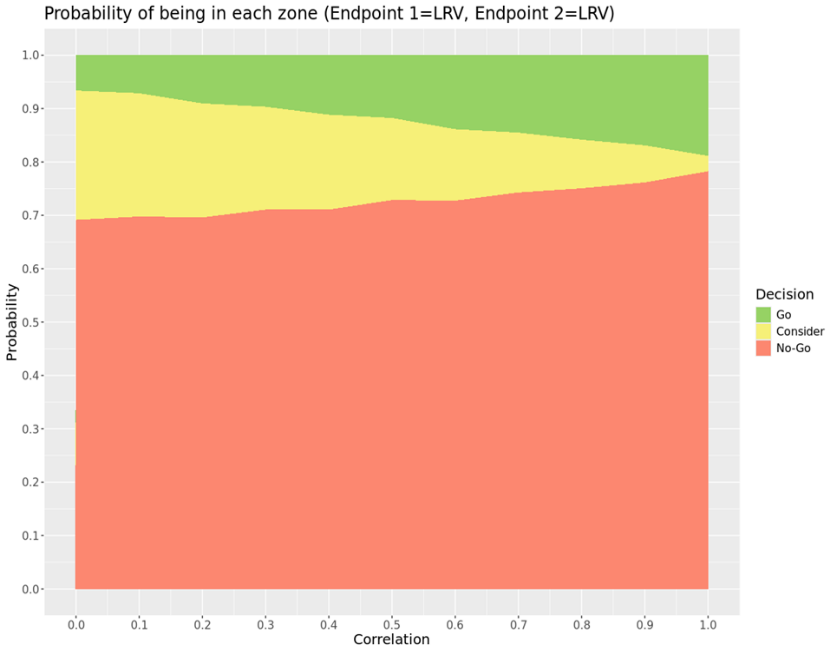


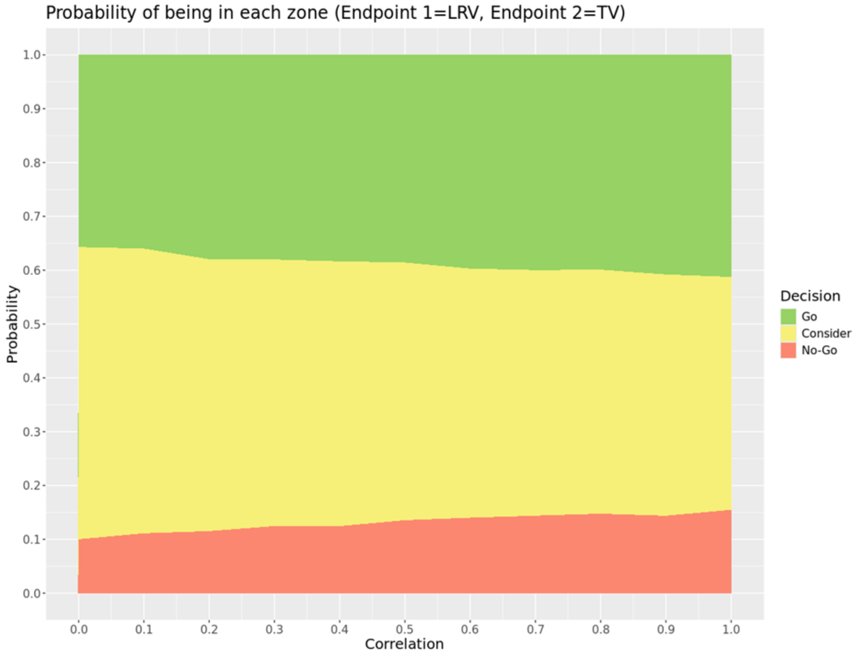
Correlation = 0.9

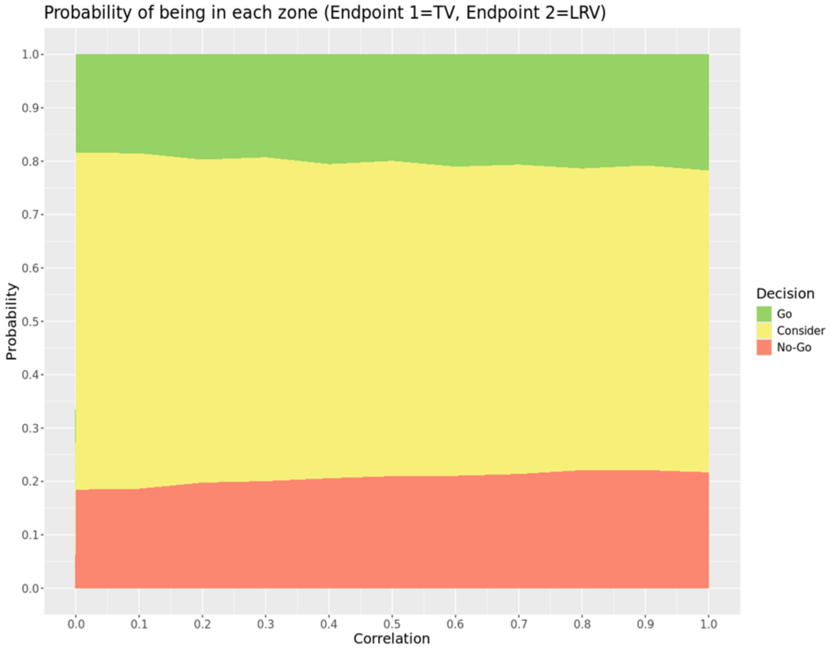


Impact of correlation

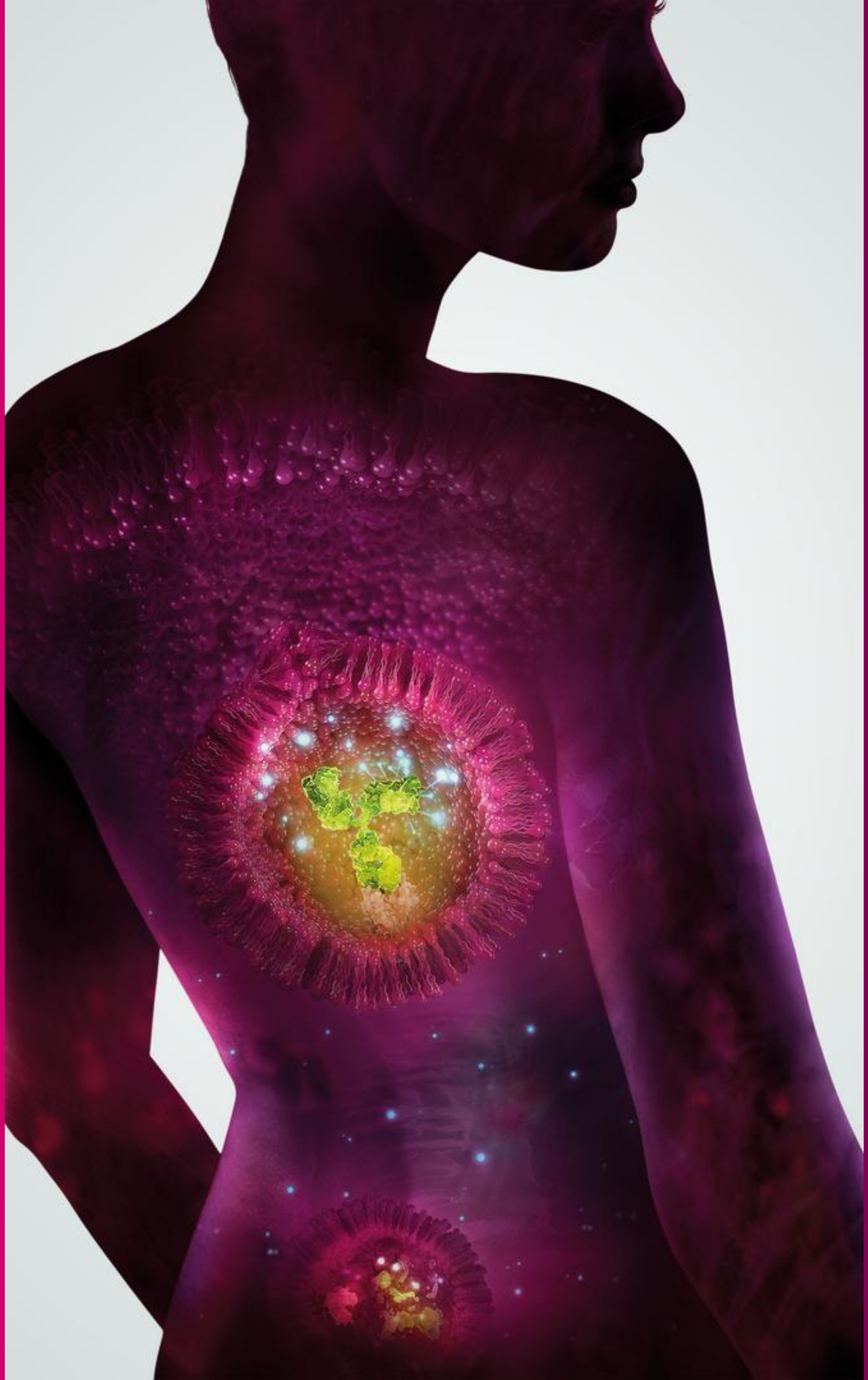




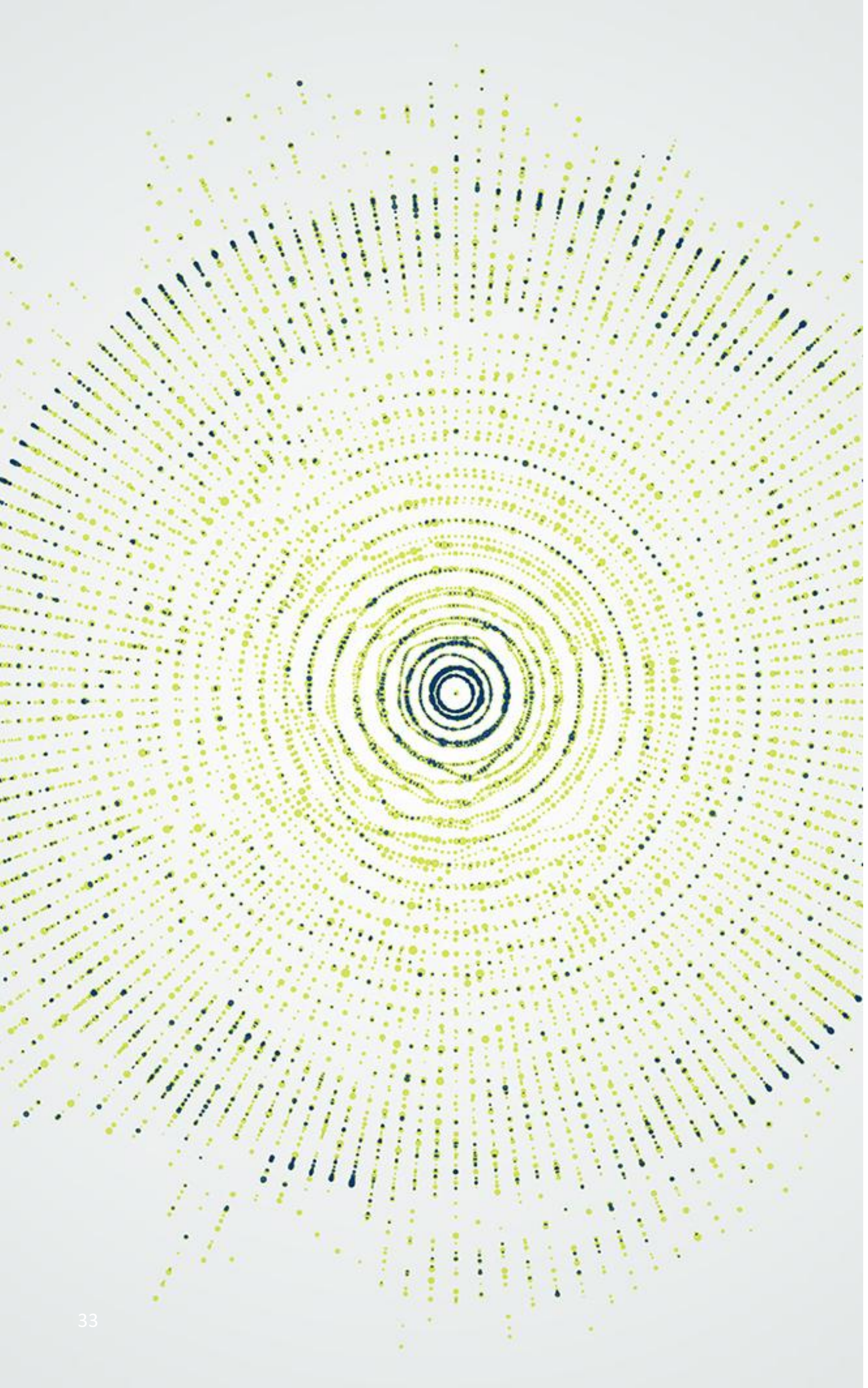




- Results are for the above example, may change under different decision matrices or different endpoint combinations
- Under TV/TV or LRV/LRV, with higher correlation
  - Consider zones become narrower
  - Slight increase in false Go and false No-Go risks. Intuitively, with high correlation, if one endpoint is a Go then the second endpoint is likely a Go as well



Potential extensions



Potential extensions

- Incorporating interim analyses
- Exploring different types of correlation
- Implementing 3+ endpoints

Thank you.

Acknowledgements

- Co-authors: Laura Barker, Em Belanger, Paul Frewer, Danny Lu

References

- [1] Frewer, P., Mitchell, P., Watkins, C., & Matcham, J. (2016). Decision-making in early clinical drug development. Pharmaceutical statistics, 15(3), 255–263. https://doi.org/10.1002/pst.1746
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- [3] Wusuo Liu, C., (2019). SimJoint: simulate joint distribution given marginals and correlation matrix, https://doi.org/10.32614/CRAN.package.SimJoint