Nested Resampling for Projecting Future Outcomes with Application to Decision-Making

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Decision making

Making investment decisions for future studies whilst existing studies are ongoing has become an increasingly quantitative exercise.

There are many examples of probabilistic decision rules expressed in either Bayesian or Frequentist frameworks.[1,2]

Criteria: General Form

A common form of decision-making rule is:

$$\text{Prob}\left(\begin{array}{c}\text{Observing some future result (or better)}\\ \text{Given the data we observe at the IA}\end{array}\right) > XX\%$$

Solutions for the univariate case are well established, but multivariate rules require the relationships between the endpoints to be carefully considered.

Case Study

Use interim data from phase 2 to determine timing of investment to develop phase 3 studies in neuropathic pain.

Decide whether to

Invest time/money whilst phase 2 completes

OR

Wait for end of phase 2 to initiate investment.

Decision to initiate investment before the end of Ph2 would be based on a positive result on one or more of three criteria.

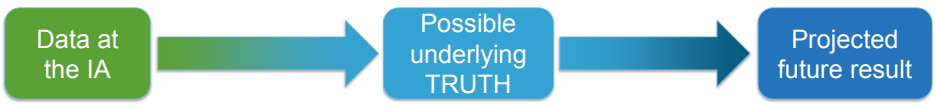
The same probability threshold was used for all 3 criteria.

Probability of at least XX% that at the end of the study :

- Difference in mean pain score > *threshold1*
- OR for pain response* > *threshold2*
- OR for "perception of change" response > *threshold3*

* combines pain score and treatment adherence

Two-step process



Allows for 2 sources of uncertainty:

- The uncertainty about the true (joint) distribution of the three endpoints
- The uncertainty about what we might observe in future results conditional on a given truth
- Assumes subjects in the IA are representative of subjects in the remainder of the study

Step 1

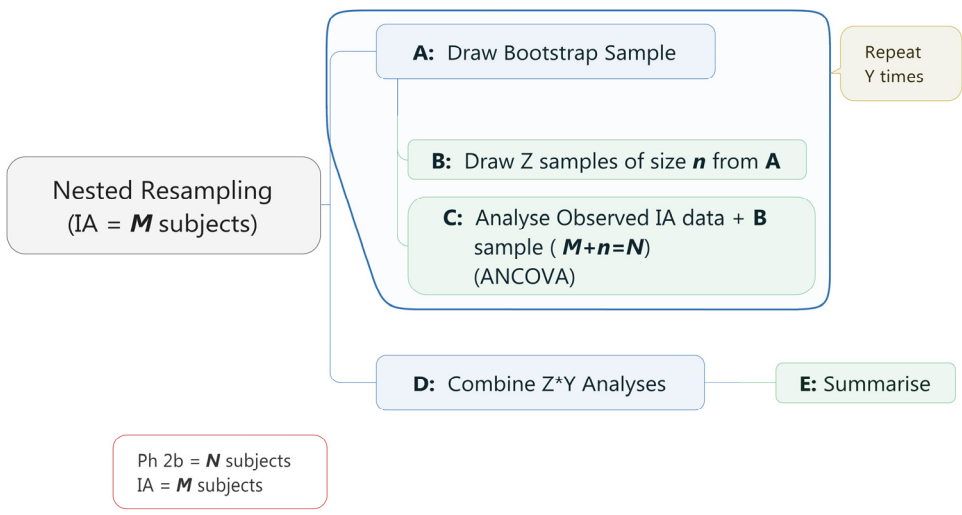
Take a series of bootstrap samples as an empirical joint distribution of "everything".

Step 2

Resample from each bootstrap draw, with size n=N-M (N = planned study sample size; M = sample size at IA).

Append to observed interim data and analyse 3 endpoints.

Implementation



Phase 2b : N= 133 subjects / arm

IA: M= 65 subjects / arm

Y = 1000 Bootstrap samples of 65 subjects / arm

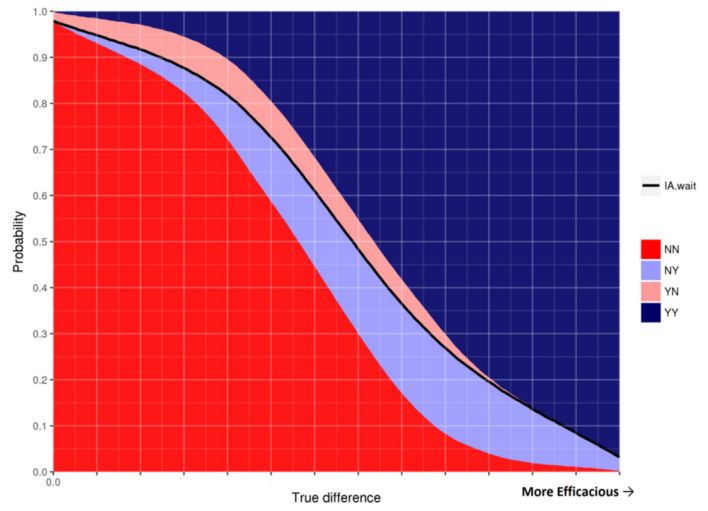
Z = 1000 resamples of 68 subjects / arm

For each criteria, count the number of analyses that meet the threshold out of the 1,000,000 resampled studies

Properties

Assess operating characteristics of this approach using 1000 simulated IA datasets for a range of scenarios.

Total of 18 Billion analyses → significant computing resource



Example properties: Probability of meeting criteria 1 at interim &/or final analysis for a range of true effects

Summary

- A resampling approach to decision rules based on multiple endpoints, where relationships are unknown
- Assumptions that are more easily understood by non-statisticians
- Avoids imposing parametric assumptions when projecting future outcomes

References

1: Richardus Vonk, Quantitative Decision Making - One Step Further; PSI Conference 2016
2: Paul Frewer, Decision Making in Early Clinical Development; PSI Conference 2016

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