Closed Form Predictive Probability for Interim Decision Making

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Aim

When exploring futility analysis, as binary data have a fixed number of outcomes the predictive probability of achieving end of study success can be calculated using a closed form approach (Dmitrienko, 2006).

Based on the predictive probabilities and a particular stopping rule, we can create and present a decision grid for each possible event outcome at the interim. This decision grid is then multiplied with the probability of events occurring under different assumptions of the true response, to provide operating characteristics without the need for simulation.

This poster aims to present a brief example to illustrate how the calculations were performed and how potential stopping rules were presented and discussed with the clinical team.

Step 1: Scenario set up

To demonstrate the concepts a hypothetical study has been set up with:

- Two treatment arms, interim at N=5 per arm, final at N=10 per arm
- End of study success defined as P(Active/Control < 1) >= 97.5
- A non-informative Beta(0.5, 0.5) prior for the final analysis

Step 2: Predictive Probability at Interim

At an interim the number of events on active and control would be known. From this we can examine the remaining 5 subjects in each arm and determine which combinations would lead to end of study success.

From this the predicted probability of seeing the post-interim results needed for end of study success can be calculated using the following formula (Dmitrienko, 2006):

$$\boldsymbol{P(t_i|s_i) = \frac{B(s_i + t_i + \alpha_i, N - s_i - t_i + \beta_i)}{(N - n - t_i)B(t_i + 1, N - n - t_i)B(s_i + \alpha_i,\ n - s_i + \beta)}}$$

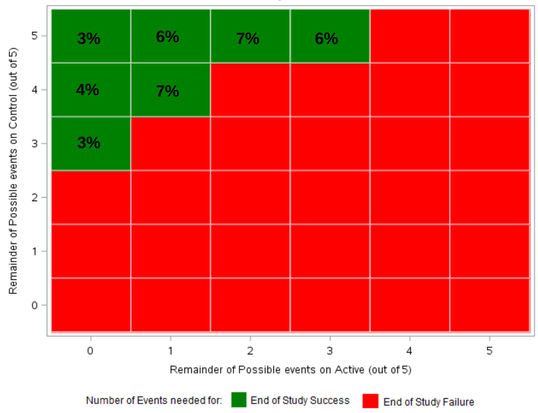
$$where:\ N = number\ of\ events\ at\ the\ end\ of\ the\ study$$
$$n = number\ of\ events\ at\ the\ interim.$$
$$s_i = number\ of\ events\ at\ interim,$$
$$t_i = number\ of\ post\ interim\ events\ (0 \le t_i \le N - n)$$
$$prior \sim B(\alpha_i, \beta_i)$$

The beta binomial distribution assumes the rate of events for the second half of the data follows the same rate observed in the first half with the inclusion of a prior.

Potential results at the interim:

Assume that at the interim we have 2 events on active and 4 events on control with a non-information Beta(1,1) prior for the predictive distribution.

The grid below presents the combination of future events that result in end of study success and failure, and the predictive probabilities of those events that lead to success occurring. Summing the possibilities that lead to success gives us a 36% predictive probability.



As the data is binary it means this process can be repeated for all possible interim outcomes. This gives a grid of predictive possibilities that can be used to test potential decision rules.

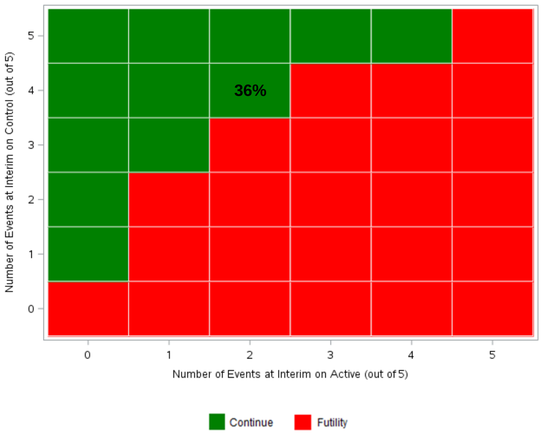
Step 3: Examining Decision Rules

This grid of predictive possibilities can now be used to examine potential decision rules. For demonstration the following rule has been used:

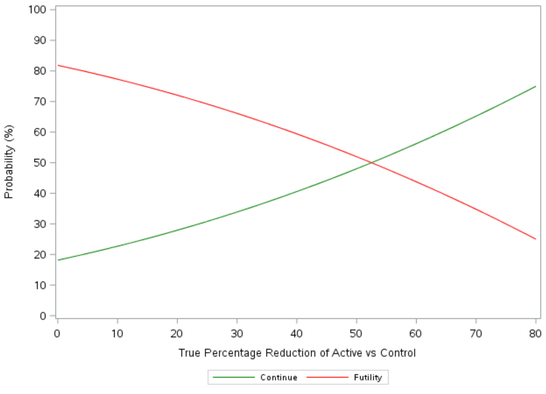
- Stop for futility if predicted probability < 20% otherwise continue.

The decision grid below gives all possible interim outcomes along with the decision under the chosen rule.

This enables clinical to review in terms of actual events and differences needed. For example, if there are two events on active there must be four or more events in the control arm in order to continue the study.



As we have the decision grid above, we can multiply each outcome by the probability of observing the number of events on active and control under different assumptions of the true response using a binomial distribution. This gives the operational characteristics shown below:



Conclusions

The main advantages of using this method are:

- Once the predictive probability for all potential outcomes (Step 2) has been created new rules can be examined within moments
- Presenting a decision grid allows clinical to review rules in terms of actual events needed and whether the difference between arms is sensible.

The main disadvantage of using this method is:

- The high upfront computational time needed to generate the predictive probability for all outcomes, however in small studies this may be no more computationally intensive than simulation.

In conclusion, despite an upfront time investment with binary data this method can lead to shorter computational times for testing potential rules along with clearer discussions with clinical teams.

References

1. Dmitrienko, A., & Wang, M. D. (2006). Bayesian predictive approach to interim monitoring in clinical trials. . *Statistics in Medicine*, 25(13), 2178-2195

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