When does an interim analysis not jeopardise the type I error rate ?

Lund University
Faculty of Medicine

Skånes universitetssjukhus

Per Broberg[1]

[1]Department of Oncology and Cancer Epidemiology, Clinical Sciences, Lund University and Skåne University Hospital, Sweden

Introduction

Interest in adaptive clinical trial designs has surged during the last few years. One particular kind of these called *sample-size adjustable designs* (sometimes sample size re-estimation designs) has come to use in a number of trials lately. Following a pre-planned interim analysis this design offers the options of

1. closing the trial due to futility
2. continuing as planned
3. continuing with an increased sample size

Recent research has identified situations when raising the sample size does not lead to inflation of the type I error rate [1]. That reference identifies a set of promising outcomes where it is safe to raise the sample size. Denote the observed test statistic at the interim by z, the originally planned sample size by N_0, the number of observations at the interim by n, and the raise considered by r. Call the final test statistic Z_2^*. Then [1] finds that the modified rejection threshold $c(z, N_0+r-n)$ ensures protection of type I error:

$$P_0(Z_2^* \geq c(z, N_0+r-n)) = \alpha, \quad (1)$$

where

$$c(z, N_0+r-n) = (N_0+r)^{-0.5}\sqrt{\frac{N_0+r-n}{N_0-n}}(z_\alpha\sqrt{N_0} - z\sqrt{n}) + z\sqrt{n}.$$

The set of promising results is defined through the inequality

$$c(z,\ N_0+r-n) \leq z_\alpha (2)$$

Solving for z in equation (1) to obtain a relation of the type $z \geq z_\alpha b'(n, N_0, r)$yields

$$b'(n, N_0, r) = \frac{\sqrt{N_0}\sqrt{\frac{N_0+r-n}{N_0-n}} - \sqrt{N_0+r}}{\sqrt{n}(\sqrt{\frac{N_0+r-n}{N_0-n}} - 1)}$$

The boundary b' will now be related to the boundary

$$b(q, V) = \frac{\sqrt{1-q} - \sqrt{1-qV}}{\sqrt{qV}\sqrt{1-q} - \sqrt{q}\sqrt{1-qV}}$$

in [2], where $q = n/(N_0+r)$ and $V = (N_0+r)/N_0$. In that reference it is proven that the type I error rate remains intact upon raising only upon having observed $\{z \geq z_\alpha b(q, V)\}$.

As explained in [2] the function b satisfies the inequalities $(1-\sqrt{1-qV})/\sqrt{qV} \leq b(q, V) \leq \sqrt{qV} = \sqrt{n/N_0}$.

We will prove b and b' to be identical. In other words: The event $\{z \geq z_\alpha b'(q, V)\}$ is identical to the event $\{z \geq z_\alpha b(q, V)\}$. Further, we will derive the lower bound of b as well as the limit at the origen of b as a function of r. The reference [2] provides a proof of the upper bound.

Result and discussions

Proof of equivalence

To simplify notation regard b' as a function of q and V, as was done for b above. In this notation it follows that $qV = \frac{n}{N_0}$. Also, $1-qV = \frac{N_0-n}{N_0}$, and, $(1-q)V = \frac{N_0+r-n}{N_0}$. Consequently,

$$\frac{N_0+r-n}{N_0-n} = \frac{N_0}{N_0-n}\frac{N_0+r-n}{N_0} = \frac{(1-q)V}{1-qV}$$

Thus, redefining b' as a function of (q, V) yields

$$b'(q, V) = \frac{\frac{1}{\sqrt{qV}}\sqrt{\frac{(1-q)V}{1-qV}} - \frac{1}{\sqrt{q}}}{\sqrt{\frac{(1-q)V}{1-qV}} - 1}$$

But multiplying both numerator and denominator by $\sqrt{1-qV}$ and elminating one V from the first term of the numerator simplifies the expression to

$$b'(q, V) = \frac{\sqrt{(1-q)} - \sqrt{1-qV}}{\sqrt{q}(\sqrt{(1-q)V} - \sqrt{1-qV})}$$

A final reshaping of the denominator shows

$$b'(q, V) = \frac{\sqrt{(1-q)} - \sqrt{1-qV}}{\sqrt{qV}\sqrt{(1-q)} - \sqrt{q}\sqrt{1-qV}} = b(q, V)$$

R code

The boundary b may be calculated with the following R code

```
B.func <- function(n, N0, r){ q <- n/(N0+r);V <- (N0+r)/N0; (sqrt(1-q)-sqrt(1-q*V))/ (sqrt(q*V)*sqrt(1-q)-sqrt(q)*sqrt(1-q*V))}
```

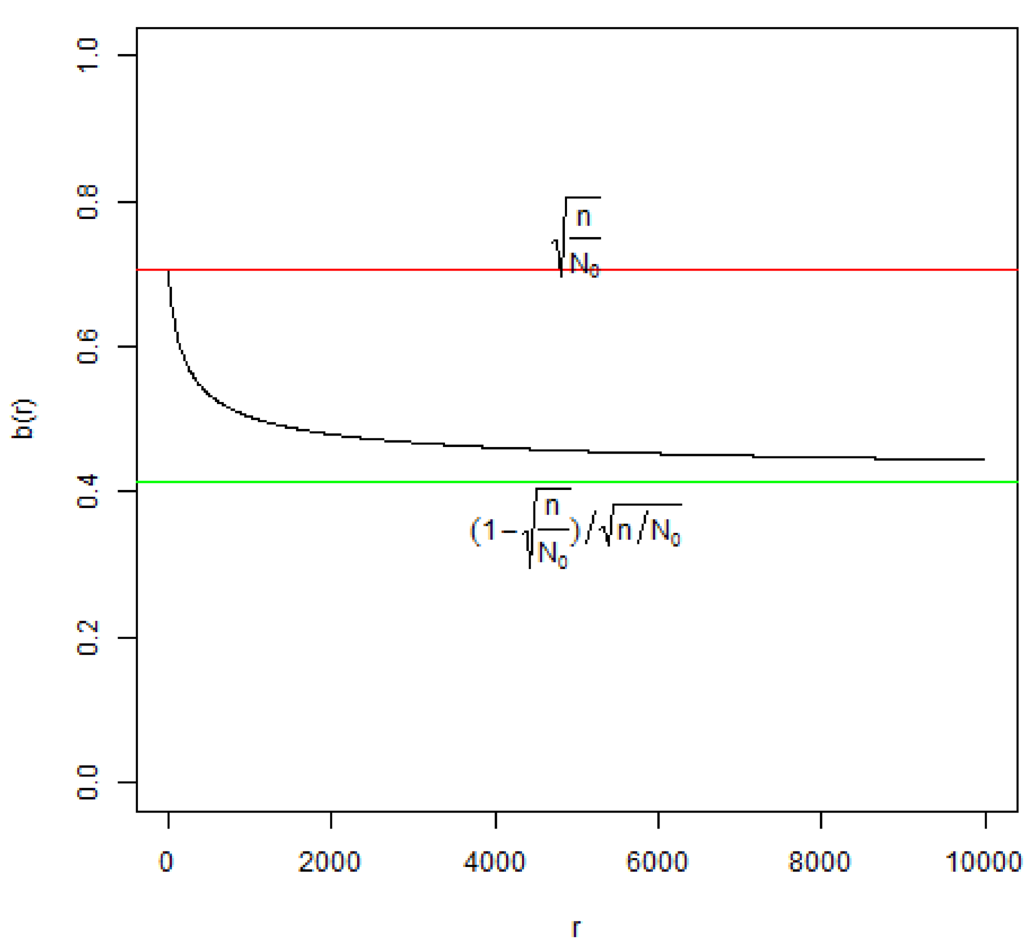

Figure: The cut-off b as a function of r given $n = 55$ and $N_0 = 110$. The upper and lower boundaries are indicated.

The function and its boundaries are displayed in Figure 1. The function is not defined in the origen but asymptotically approaches $\sqrt{n/N_0}$ as explained in the next subsection.

Limits of b

Letting r tend to infinity makes q approach zero, while qV remains unchanged. Thus in the limit b tends to $1 - \sqrt{1-qV}/\sqrt{qV}$

The limit at the origen follows from an application of l'Hôpital's rule, which enables us to look at the limit of the ratio of the derivatives of the numerator and denominator. The limit of b at the origen will be found through Taylor expansion at origen of the numerator and denominator separately. The derivative of the numerator and denominator with respect to r yields the expression

$$\frac{\frac{n}{2(N_0+r)^2\sqrt{1-\frac{n}{N_0+r}}}}{\frac{n\sqrt{n/N_0}}{2(N_0+r)^2\sqrt{1-n/(N_0+r)}} + \frac{n\sqrt{N_0+r}}{2N_0^2\sqrt{n}}\sqrt{1-n/N_0}}.$$

Evaluated at $r = 0$ and after some simplification the expression becomes

$$\lim_{r \searrow 0} b(r) = \frac{1}{\sqrt{\frac{n}{N_0}} + \sqrt{\frac{N_0}{n}}(1-\frac{n}{N_0})} = \sqrt{\frac{n}{N_0}}$$

Summary and conclusions

The decision at the interim look wether or not to raise the sample size only requires calculation of a test statistic which (approximately) follows a standard normal distribution. The theory for this has shown that the type I error rate remains intact if the results show promise, meaning that the test statistic exceeds a threshold which depends on the number of observations at the interim, the planned final sample size and the increase considered.

References

[1] Mehta CR, Pocock SJ: **Adaptive increase in sample size when interim results are promising: A practical guide with examples.** *Stat Med* 2011, **30**(28):3267–3284, [http://dx.doi.org/10.1186/1471-2288-13-94

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