

Logistics of Running a Multc Trial

This note explains the details of running a single-arm phase II trial that was designed using the safety monitoring method of Thall, Simon, and Estey. [1]

Stopping boundaries for toxicity

First we consider a trial with an early stopping rule only for toxicity. Suppose a trial of 10 patients with a minimum sample size of 5 patients has the following toxicity stopping boundary according to the Multc Lean Desktop software [2]:

The following table describes the toxicity stopping boundary.
To use it:

1. Find your number of patients in the left-side column.
(the range is inclusive)
2. The trial should be stopped if the number of toxicities is in the range in the right-side column.
(the range is inclusive)

Note that if the trial should continue or stop regardless of the number of toxicities, this is indicated in the right-side column instead of a toxicity range.

Note also that this full toxicity stopping boundary may include stopping conditions which are logically impossible to reach if the trial is conducted properly.

	Stop the trial if there are this many toxicities total:
# Patients (inclusive)	# Toxicities (inclusive)
1-4	Never stop with this many patients
5	3-5
6	4-6
7-8	5-8
9	6-11
10	Always stop with this many patients

In this example, the first opportunity for the trial to stop is at five patients. If three or more out of the first five patients were toxic, the trial will stop. Likewise the trial will stop if four or more out of the first six patients were toxic, or five or more out of the first eight, etc.

Here are three scenarios to show how the first opportunity for the trial to stop might play out.

1. Suppose the first three patients were toxic. Then we know that the trial will stop at five patients, because there will be at least three toxicities out of the first five patients. The decision of whether to stop the trial at three patients, knowing that the trial will stop at the minimum sample size of five regardless of the outcomes for the fourth and fifth patients, is beyond the scope of the software because the minimum sample size was specified to be five patients.
2. Next, suppose the first three patients were not toxic. Then we know that we will have at most two toxicities out of the first five patients, and thus the trial will not stop at five patients. In fact, we know the trial will not stop at six patients either: we can't have four toxicities out of the first six if at least three of the first six were not toxic.
3. Finally, suppose the first two patients were toxic and the next two were not. We go ahead and treat the fifth patient, but then we wait. We have to know how the fifth patient turns out to know whether we stop.

These three examples are typical. Most often, it is possible to know before reaching a certain number of patients whether the stopping rule will apply, as in scenarios (1) and (2). Occasionally one will have to pause accrual at a certain number of patients in order to know whether to continue, as in scenario (3). In practice, one seldom need to pause long or pause at all, and so monitoring rules do not have much effect on the time needed to run a trial. [3]

Note that similar considerations apply when accruing patients in a trial with a cohort size greater than one. It may be possible before the current cohort is complete to determine whether the trial will stop or continue after the current cohort is complete.

The decision of whether to stop before the minimum sample size or the current cohort has been completely accrued, when it is known that the trial will stop after the minimum sample size or the current cohort has been completely accrued, is beyond the scope of this application. We do wish to point out however that in some cases it is possible to know, before all the patients' outcomes are known, whether or not the stopping criteria will be reached. We also wish to point out that our investigations indicate that having to pause accrual while waiting for patient outcomes to become known, due to the monitoring rules, does not have much effect on the time needed to run a trial. [3]

Stopping boundary for response (efficacy)

Next we look at response (efficacy) stopping boundary, the conditions under which a trial will stop early due to an experimental treatment being less effective than the standard treatment. Suppose we are given the following response stopping boundary:

The following table describes the response stopping boundary.
To use it:

1. Find your number of patients in the left-side column.
(the range is inclusive)
2. The trial should be stopped if the number of responses is in the range in the right-side column.
(the range is inclusive)

Note that if the trial should continue or stop regardless of the number of responses, this is indicated in the right-side column instead of a response range.

Note also that this full response stopping boundary may include stopping conditions which are logically impossible to reach if the trial is conducted properly.

	Stop the trial if there are this many responses total:
# Patients (inclusive)	# Responses (inclusive)
1-7	Never stop with this many patients
8-11	0
12-15	0-1
16-19	0-2
20	Always stop with this many patients

In this example, the first opportunity for the trial to stop is at eight patients. If none of the first eight patients were to respond, the trial will stop. Likewise the trial will stop if one or fewer out of the first twelve patients were to respond, or two or fewer out of the first sixteen, etc.

As with toxicity boundaries, one can often know in advance whether a trial will meet the stopping criteria. For example, if two out of the first six patients responded in this example then we know the trial will continue at least through the fifteenth patient.

A trial will often have both a toxicity and a response stopping boundary. In this case the trial stops if either criterion indicates it should stop.

References

[1] Peter Thall, Richard Simon, and Elihu Estey in "Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes", *Statistics in Medicine*, vol 14, 357-379 (1995).

[2] MDACC Biostatistics and Applied Mathematics software download site.

<https://biostatistics.mdanderson.org/SoftwareDownload>.

Multc Lean is a Windows program for designs monitoring only response and toxicity.

Multc99 is a DOS program for more complex designs.

[3] John Cook. Simulation Results for Phase II Clinical Trial Durations. Technical report [UTMDABTR-014-04](#).