Multc99 Phase IIa vs. Multc Lean Desktop versions 1.2 and 2.0 Stopping Boundaries

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Introduction

Multc99 and Multc Lean Desktop are both software packages which can be used to design clinical trials monitoring response (efficacy) and toxicity (safety) and both produce stopping boundaries for these outcomes. I wish to illustrate that the same stopping conditions are displayed in different ways by Multc99 and Multc Lean Desktop versions 1.2 and 2.0. The differences between the Multc99 and the Multc Lean Desktop v. 1.2 display formats have led to great confusion, since even when they describe the same stopping boundary they can look quite different. We hope that the display format used by Multc Lean Desktop v. 2.0 is clear and unambiguous, and an improvement over the other formats.

In order to illustrate the differences and similarities between the three ways of displaying the stopping boundaries, I constructed two very similar but artificial trial designs to be used with Multc99's Phase IIa component and Multc Lean Desktop. I chose these designs to be as similar as possible, and also brief.

One key difference between the Multc99 Phase IIa component and Multc Lean Desktop is the calculation used to determine the stopping boundary. Both applications determine that the stopping criterion has been met when a calculated probability, involving the posterior distribution of the experimental rate of the event in question, has gone beyond a threshold. In the case of Multc99's Phase IIa design, the calculated probability is the probability that a realization from the posterior distribution of the experimental rate is greater than a *constant*. In the case of Multc Lean Desktop, the calculated probability is the probability that a random variable from *another distribution* (the standard or historical distribution of the rate of the event) is greater than (in the case of response) or less than (in the case of toxicity) a random variable from the posterior distribution of the experimental rate. See Calculations for more discussion of this.

The trial design presented here was chosen so that these two different probability calculations lead to the same conclusions regarding the stopping criteria. This was done to make the comparison of stopping boundary outputs clearer, but it should be borne in mind that in general these different calculations result in slightly different stopping boundaries.

Example Trial Design

The trial design is as follows:

For both Multc99 Phase IIa and Multc Lean Desktop:

- The minimum number of patients is 1.
- The maximum number of patients is 15.
- The prior distribution on the experimental rate of each event is a Beta(1, 1) distribution.
- The stopping criteria threshold is at the 0.95 level for both events.
    - For Multc99, this means that the efficacy (response) threshold is 0.05 and the adverse (toxicity) threshold is 0.95.
    - For Multc Lean Desktop, this means that both toxicity and response thresholds are 0.95.

For Multc99 Phase IIa:

- The standard or historical rate, to which the posterior distribution of the experimental rate of either event is compared, is a **constant set to 0.5**.

For Multc Lean Desktop:

- The standard to which the posterior distribution of the experimental rate of either event is compared is a **Beta(1000, 1000) distribution**. This has a mean of 0.5 and a standard deviation of approximately 0.01118. Its parameters are each at the maximum that is allowed by Multc Lean Desktop.
- The delta (or “shift” or “slip”) parameter is 0 for both outcomes. Multc99 Phase IIa doesn’t use such a parameter.

Stopping Boundary Output

Response Stopping Boundaries

Multc99 Phase IIa Response Stopping Boundary

The following is the output from Multc99 Phase IIa:

```
Boundary (lower bounds):

 -1/ 1

  0/ 4

  1/ 7

  2/10

  3/12
```

I believe these should be interpreted in the following way:

- For 1 through 3 patients, there is no stopping boundary for response. The value of -1 response in 1 patient is essentially a placeholder.
- For 4 through 6 patients, the stopping boundary is 0 responses.
- For 7 through 9 patients, the stopping boundary is 1 or fewer responses.
- For 10 through 11 patients, the stopping boundary is 2 or fewer responses.
- For 12 through 15 (the maximum) patients, the stopping boundary is 3 or fewer responses (but it is implicit that one would stop at 15 patients, the maximum).

Table 1 shows the calculations used by Multc99 Phase IIa to construct this boundary, but for all possible response data. In this case, to make comparisons with Multc Lean Desktop easier, I am displaying the complements of the probabilities that Multc99 Phase IIa actually calculates, and comparing them to the complement of the cutoff probability. Thus whereas Multc99 Phase IIa calculates a probability P and determines that the trial should stop if P is below 0.05, here I am reporting (1-P) for the calculated values and indicate that the trial should stop if (1-P) is greater than (1-0.05) = 0.95. The cells corresponding to data indicating that the trial should continue are colored blue, while the cells corresponding to data indicating that the trial should stop are colored red. The cells corresponding to the boundary points reported by Multc99 Phase IIa are outlined, except the first one, which I omit as it is essentially a placeholder. You can see that Multc99 reports the cells where the boundary, thought of as a step function of number of patients, increases.

Table 1: Multc99 Phase IIa Response Stopping Calculations (Complementary) and Boundary

		Patients														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Responses	0	0/1: .7500	0/2: .8750	0/3: .9375	0/4: .9688	0/5: .9844	0/6: .9922	0/7: .9961	0/8: .9980	0/9: .9990	0/10: .9995	0/11: .9998	0/12: .9999	0/13: .9999	0/14: 1.0000	0/15: 1.0000
	1	1/1: .2500	1/2: .5000	1/3: .6875	1/4: .8125	1/5: .8906	1/6: .9375	1/7: .9648	1/8: .9805	1/9: .9893	1/10: .9941	1/11: .9968	1/12: .9983	1/13: .9991	1/14: .9995	1/15: .9997
	2	NA	2/2: .1250	2/3: .3125	2/4: .5000	2/5: .6563	2/6: .7734	2/7: .8555	2/8: .9102	2/9: .9453	2/10: .9673	2/11: .9807	2/12: .9888	2/13: .9935	2/14: .9963	2/15: .9979
	3	NA	NA	3/3: .0625	3/4: .1875	3/5: .3438	3/6: .5000	3/7: .6367	3/8: .7461	3/9: .8281	3/10: .8867	3/11: .9270	3/12: .9539	3/13: .9713	3/14: .9824	3/15: .9894
	4	NA	NA	NA	4/4: .0313	4/5: .1094	4/6: .2266	4/7: .3633	4/8: .5000	4/9: .6230	4/10: .7256	4/11: .8062	4/12: .8666	4/13: .9102	4/14: .9408	4/15: .9616
	5	NA	NA	NA	NA	5/5: .0156	5/6: .0625	5/7: .1445	5/8: .2539	5/9: .3770	5/10: .5000	5/11: .6128	5/12: .7095	5/13: .7880	5/14: .8491	5/15: .8949
	6	NA	NA	NA	NA	NA	6/6: .0078	6/7: .0352	6/8: .0898	6/9: .1719	6/10: .2744	6/11: .3872	6/12: .5000	6/13: .6047	6/14: .6964	6/15: .7728
	7	NA	NA	NA	NA	NA	NA	7/7: .0039	7/8: .0195	7/9: .0547	7/10: .1133	7/11: .1938	7/12: .2905	7/13: .3953	7/14: .5000	7/15: .5982
	8	NA	NA	NA	NA	NA	NA	NA	8/8: .0020	8/9: .0107	8/10: .0327	8/11: .0730	8/12: .1334	8/13: .2120	8/14: .3036	8/15: .4018
	9	NA	NA	NA	NA	NA	NA	NA	NA	9/9: .0010	9/10: .0059	9/11: .0193	9/12: .0461	9/13: .0898	9/14: .1509	9/15: .2272
	10	NA	NA	NA	NA	NA	NA	NA	NA	NA	10/10: .0005	10/11: .0032	10/12: .0112	10/13: .0287	10/14: .0592	10/15: .1051
	11	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	11/11: .0002	11/12: .0017	11/13: .0065	11/14: .0176	11/15: .0384
	12	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	12/12: .0001	12/13: .0009	12/14: .0037	12/15: .0106
	13	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	13/13: .0001	13/14: .0005	13/15: .0021
	14	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	14/14: .0000	14/15: .0003
	15	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	15/15: .0000

Multc Lean Desktop v. 1.2 Response Stopping Boundary

The following is the v. 1.2 output from Multc Lean Desktop:

The following are less-than-or-equal boundaries:
a pair (n, m) means to stop if the number of responses after treating (m) patients is less than or equal to (n).
NOTE: If there is no boundary given for a value of (m) patients, this means that it is impossible to stop for response at that number of patients given that the trial has not stopped previously.

n (# responses)	m (# patients)
0	4
1	7
2	10
3	12
4	15

This should be interpreted in the following way:

- At 4 patients, if there are no responses, stop.
- At 7 patients, if there are 1 or fewer responses, stop.
- At 10 patients, if there are 2 or fewer responses, stop.
- At 12 patients, if there are 3 or fewer responses, stop.
- Stop at 15 patients (the maximum). The value of 4 responses in 15 patients is essentially a placeholder.

Table 2 shows the calculations involved in generating this representation, but for all possible response data. The cells corresponding to data indicating that the trial should continue are colored blue, while the cells corresponding to data indicating that the trial should stop are colored red. The cells corresponding to the boundary points reported by Multc Lean Desktop v. 1.2 are outlined. One can think of the conduct of a trial as moving from cell to cell as additional patients are accrued. If so, then accruing an additional patient with a response is equivalent to moving one cell diagonally down and to the right. Accruing an additional patient with no response is equivalent to moving one cell directly to the right. Thinking about this, it is easy to see that the only places where a trial can move from continuing (a blue cell) to stopping (a red cell) before the maximum number of patients have been accrued are exactly the same as the outlined cells. So it is easy to see that this representation shows the circumstances under which the trial can stop.

Table 2: Multc Lean Desktop Response Stopping Calculations with v. 1.2 Boundary

Responses	Patients														
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
0	0/1: .7499	0/2: .8748	0/3: .9373	0/4: .9686	0/5: .9843	0/6: .9921	0/7: .9960	0/8: .9980	0/9: .9990	0/10: .9995	0/11: .9997	0/12: .9999	0/13: .9999	0/14: 1.0000	0/15: 1.0000
1	1/1: .2501	1/2: .5000	1/3: .6873	1/4: .8122	1/5: .8903	1/6: .9372	1/7: .9646	1/8: .9803	1/9: .9891	1/10: .9940	1/11: .9968	1/12: .9982	1/13: .9991	1/14: .9995	1/15: .9997
2	**NA**	2/2: .1252	2/3: .3127	2/4: .5000	2/5: .6560	2/6: .7730	2/7: .8550	2/8: .9097	2/9: .9449	2/10: .9669	2/11: .9804	2/12: .9886	2/13: .9934	2/14: .9962	2/15: .9978
3	**NA**	**NA**	3/3: .0627	3/4: .1878	3/5: .3440	3/6: .5000	3/7: .6364	3/8: .7456	3/9: .8275	3/10: .8861	3/11: .9264	3/12: .9533	3/13: .9709	3/14: .9821	3/15: .9891
4	**NA**	**NA**	**NA**	4/4: .0314	4/5: .1097	4/6: .2270	4/7: .3636	4/8: .5000	4/9: .6227	4/10: .7250	4/11: .8054	4/12: .8658	4/13: .9095	4/14: .9401	4/15: .9610
5	**NA**	**NA**	**NA**	**NA**	5/5: .0157	5/6: .0628	5/7: .1450	5/8: .2544	5/9: .3773	5/10: .5000	5/11: .6125	5/12: .7088	5/13: .7872	5/14: .8482	5/15: .8940
6	**NA**	**NA**	**NA**	**NA**	**NA**	6/6: .0079	6/7: .0354	6/8: .0903	6/9: .1725	6/10: .2750	6/11: .3875	6/12: .5000	6/13: .6044	6/14: .6957	6/15: .7718
7	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	7/7: .0040	7/8: .0197	7/9: .0551	7/10: .1139	7/11: .1946	7/12: .2912	7/13: .3956	7/14: .5000	7/15: .5978
8	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	8/8: .0020	8/9: .0109	8/10: .0331	8/11: .0736	8/12: .1342	8/13: .2128	8/14: .3043	8/15: .4022
9	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	9/9: .0010	9/10: .0060	9/11: .0196	9/12: .0467	9/13: .0905	9/14: .1518	9/15: .2282
10	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	10/10: .0005	10/11: .0032	10/12: .0114	10/13: .0291	10/14: .0599	10/15: .1060
11	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	11/11: .0003	11/12: .0018	11/13: .0066	11/14: .0179	11/15: .0390
12	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	12/12: .0001	12/13: .0009	12/14: .0038	12/15: .0109
13	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	13/13: .0001	13/14: .0005	13/15: .0022
14	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	14/14: .0000	14/15: .0003
15	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	15/15: .0000

Multc Lean Desktop v. 2.0 Response Stopping Boundary

The following is the v. 2.0 output from Multc Lean Desktop:

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)**
1-3	Never stop with this many patients
4-6	0
7-9	0-1
10-11	0-2
12-14	0-3
15	Always stop with this many patients

I hope that this table is self-explanatory.

Table 3 is the same as Table 2, but with all the conditions covered in the v. 2.0 table outlined. You can see that the table covers all the possible stopping conditions – both those in which the stopping rule would be invoked and those for which the number of patients is the maximum.

Table 3: Multc Lean Desktop Response Stopping Calculations with v. 2.0 Boundary

Responses	Patients 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
0	0/1: .7499	0/2: .8748	0/3: .9373	0/4: .9686	0/5: .9843	0/6: .9921	0/7: .9960	0/8: .9980	0/9: .9990	0/10: .9995	0/11: .9997	0/12: .9999	0/13: .9999	0/14: 1.0000	0/15: 1.0000
1	1/1: .2501	1/2: .5000	1/3: .6873	1/4: .8122	1/5: .8903	1/6: .9372	1/7: .9646	1/8: .9803	1/9: .9891	1/10: .9940	1/11: .9968	1/12: .9982	1/13: .9991	1/14: .9995	1/15: .9997
2	NA	2/2: .1252	2/3: .3127	2/4: .5000	2/5: .6560	2/6: .7730	2/7: .8550	2/8: .9097	2/9: .9449	2/10: .9669	2/11: .9804	2/12: .9886	2/13: .9934	2/14: .9962	2/15: .9978
3	NA	NA	3/3: .0627	3/4: .1878	3/5: .3440	3/6: .5000	3/7: .6364	3/8: .7456	3/9: .8275	3/10: .8861	3/11: .9264	3/12: .9533	3/13: .9709	3/14: .9821	3/15: .9891
4	NA	NA	NA	4/4: .0314	4/5: .1097	4/6: .2270	4/7: .3636	4/8: .5000	4/9: .6227	4/10: .7250	4/11: .8054	4/12: .8658	4/13: .9095	4/14: .9401	4/15: .9610
5	NA	NA	NA	NA	5/5: .0157	5/6: .0628	5/7: .1450	5/8: .2544	5/9: .3773	5/10: .5000	5/11: .6125	5/12: .7088	5/13: .7872	5/14: .8482	5/15: .8940
6	NA	NA	NA	NA	NA	6/6: .0079	6/7: .0354	6/8: .0903	6/9: .1725	6/10: .2750	6/11: .3875	6/12: .5000	6/13: .6044	6/14: .6957	6/15: .7718
7	NA	NA	NA	NA	NA	NA	7/7: .0040	7/8: .0197	7/9: .0551	7/10: .1139	7/11: .1946	7/12: .2912	7/13: .3956	7/14: .5000	7/15: .5978
8	NA	NA	NA	NA	NA	NA	NA	8/8: .0020	8/9: .0109	8/10: .0331	8/11: .0736	8/12: .1342	8/13: .2128	8/14: .3043	8/15: .4022
9	NA	NA	NA	NA	NA	NA	NA	NA	9/9: .0010	9/10: .0060	9/11: .0196	9/12: .0467	9/13: .0905	9/14: .1518	9/15: .2282
10	NA	NA	NA	NA	NA	NA	NA	NA	NA	10/10: .0005	10/11: .0032	10/12: .0114	10/13: .0291	10/14: .0599	10/15: .1060
11	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	11/11: .0003	11/12: .0018	11/13: .0066	11/14: .0179	11/15: .0390
12	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	12/12: .0001	12/13: .0009	12/14: .0038	12/15: .0109
13	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	13/13: .0001	13/14: .0005	13/15: .0022
14	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	14/14: .0000	14/15: .0003
15	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	15/15: .0000

Comparisons between the Response Stopping Boundary Representations

It is our belief that these three different approaches reflect different but complementary representations of the same stopping boundaries. In the discussion below, general statements about the boundaries are made with the assumption that the trial has a cohort size of one. These statements are not necessarily true for the situation where the cohort size is greater than one. The Multc99 Phase IIa component does not allow cohorts of greater than one patient, although Multc99 does allow this for other trial designs. Multc Lean Desktop allows cohorts of greater than one. However, for simplicity and clarity the discussion below assumes a cohort size of one.

All three representations describe the same stopping conditions, but our interpretation of the natures of the representations are:

- **Multc99:** The pairs of numbers represent the places in terms of numbers of patients where the stopping boundary in numbers of responses increases. Thus at 4 patients the boundary is 0 responses, at 7 patients it increases to 1 response, at 10 patients it increases to 2 responses, etc. The intent is to describe the boundary as step function in terms of numbers of patients.
- **Multc Lean Desktop v. 1.2:** The pairs of numbers represent the conditions under which the trial can actually stop if it is conducted correctly and it has not stopped previously. Thus it can stop at 4 patients if there are 0 responses, it can stop at 7 patients if there are 1 or fewer responses, it can stop at 10 patients if there are two or fewer responses, etc. Note that for example if the trial has accrued 8 patients, there must have been more than 1 response at 7 patients, and thus the next opportunity for the trial to stop is only at 10 patients, where more than 2 responses is required – it cannot stop at 9 patients if it did not stop at 7 patients.
- **Multc Lean Desktop v. 2.0:** The table describes all conditions under which the trial should stop, whether or not it is possible for the trial to stop under those conditions if it is conducted correctly and has not stopped previously. In particular, it describes for every possible number of patients the conditions under which the trial should stop, if any. The intent is to make the stopping conditions as clear and explicit as possible, so there is no ambiguity about the conditions under which a trial should stop, particularly for numbers of patients at which the boundary does not change and at which it is not possible for the trial to stop if it is conducted correctly and has not stopped previously. The stopping conditions for these numbers of patients is left implicit in the other representations, and although these stopping conditions can be determined from the other representations, it is not always immediately obvious how to do so, leading to confusion in some cases.

Discussion

In the case of a response stopping boundary, the numbers of patients at which the boundary increases are the same as the numbers of patients at which the trial can stop. Because the number of responses should never decrease as the trial progresses, the only way the trial can stop is if the boundary exceeds the current number of responses. Thus the Multc99 and the Multc Lean Desktop v1.2 response stopping boundary outputs are essentially the same. Also, it can be determined that between the numbers of patients at which the trial can stop, the stopping boundary should remain constant at the number of responses for the earlier (lower) number of patients. Thus it is relatively straightforward to determine

the Multc Lean Desktop v. 2.0 table from either of the other response stopping boundary representations.

The situation for the toxicity boundary is different though, as will be shown below.

Toxicity Stopping Boundaries

Multc99 Phase IIa Toxicity Stopping Boundary

The following is the output from Multc99 Phase IIa:

```
Boundary (upper bounds):

 100/ 1

  4/ 4

  5/ 5

  6/ 6

  7/ 8

  8/ 9

  9/11

 10/13

 11/14
```

I believe these should be interpreted in the following way:

- For 1 through 3 patients, there is no stopping boundary for toxicity. The value of 100 toxicities in 1 patient is essentially a placeholder.
- For 4 patients, the stopping boundary is 4 toxicities.
- For 5 patients, the stopping boundary is 5 toxicities.
- For 6 through 7 patients, the stopping boundary is 6 or more toxicities.
- For 8 patients, the stopping boundary is 7 or more toxicities.
- For 9 through 10 patients, the stopping boundary is 8 or more toxicities.
- For 11 through 12 patients, the stopping boundary is 9 or more toxicities.
- For 13 patients, the stopping boundary is 10 or more toxicities.
- For 14 through 15 (the maximum) patients, the stopping boundary is 11 or more toxicities (but it is implicit that one would stop at 15 patients, the maximum).

Table 4 shows the calculations used by Multc99 Phase IIa to construct this boundary, but for all possible toxicity data. The cells corresponding to data indicating the trial should continue are colored blue, while the cells corresponding to data indicating that the trial should stop are colored red. The cells corresponding to the boundary points reported by Multc99 Phase IIa are outlined, except the first one, which I omit as it is essentially a placeholder. You can see that Multc99 reports the cells where the boundary, thought of as a step function of number of patients, increases.

Table 4: Multc99 Phase IIa Toxicity Stopping Calculations and Boundary

Toxicities	Patients														
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
0	0/1: .2500	0/2: .1250	0/3: .0625	0/4: .0313	0/5: .0156	0/6: .0078	0/7: .0039	0/8: .0020	0/9: .0010	0/10: .0005	0/11: .0002	0/12: .0001	0/13: .0001	0/14: .0000	0/15: .0000
1	1/1: .7500	1/2: .5000	1/3: .3125	1/4: .1875	1/5: .1094	1/6: .0625	1/7: .0352	1/8: .0195	1/9: .0107	1/10: .0059	1/11: .0032	1/12: .0017	1/13: .0009	1/14: .0005	1/15: .0003
2	**NA**	2/2: .8750	2/3: .6875	2/4: .5000	2/5: .3438	2/6: .2266	2/7: .1445	2/8: .0898	2/9: .0547	2/10: .0327	2/11: .0193	2/12: .0112	2/13: .0065	2/14: .0037	2/15: .0021
3	**NA**	**NA**	3/3: .9375	3/4: .8125	3/5: .6563	3/6: .5000	3/7: .3633	3/8: .2539	3/9: .1719	3/10: .1133	3/11: .0730	3/12: .0461	3/13: .0287	3/14: .0176	3/15: .0106
4	**NA**	**NA**	**NA**	4/4: .9688	4/5: .8906	4/6: .7734	4/7: .6367	4/8: .5000	4/9: .3770	4/10: .2744	4/11: .1938	4/12: .1334	4/13: .0898	4/14: .0592	4/15: .0384
5	**NA**	**NA**	**NA**	**NA**	5/5: .9844	5/6: .9375	5/7: .8555	5/8: .7461	5/9: .6230	5/10: .5000	5/11: .3872	5/12: .2905	5/13: .2120	5/14: .1509	5/15: .1051
6	**NA**	**NA**	**NA**	**NA**	**NA**	6/6: .9922	6/7: .9648	6/8: .9102	6/9: .8281	6/10: .7256	6/11: .6128	6/12: .5000	6/13: .3953	6/14: .3036	6/15: .2272
7	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	7/7: .9961	7/8: .9805	7/9: .9453	7/10: .8867	7/11: .8062	7/12: .7095	7/13: .6047	7/14: .5000	7/15: .4018
8	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	8/8: .9980	8/9: .9893	8/10: .9673	8/11: .9270	8/12: .8666	8/13: .7880	8/14: .6964	8/15: .5982
9	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	9/9: .9990	9/10: .9941	9/11: .9807	9/12: .9539	9/13: .9102	9/14: .8491	9/15: .7728
10	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	10/10: .9995	10/11: .9968	10/12: .9888	10/13: .9713	10/14: .9408	10/15: .8949
11	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	11/11: .9998	11/12: .9983	11/13: .9935	11/14: .9824	11/15: .9616
12	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	12/12: .9999	12/13: .9991	12/14: .9963	12/15: .9894
13	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	13/13: .9999	13/14: .9995	13/15: .9979
14	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	14/14: 1.0000	14/15: .9997
15	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	15/15: 1.0000

Multc Lean Desktop v. 1.2 Toxicity Stopping Boundary

The following is the v. 1.2 output from Multc Lean Desktop:

The following are greater-than-or-equal boundaries:
a pair (n, m) means to stop if the number of toxicities after treating (m) patients is greater than or equal to (n).
NOTE: If there is no boundary given for a value of (m) patients, this means that it is impossible to stop for toxicity at that number of patients given that the trial has not stopped previously.

n (# toxicities)	m (# patients)
4	4
6	7
8	10
9	12
11	15

This should be interpreted in the following way:

- At 4 patients, if there are 4 toxicities, stop.
- At 7 patients, if there are 6 or more toxicities, stop.
- At 10 patients, if there are 8 or more toxicities, stop.
- At 12 patients, if there are 9 or more toxicities, stop.
- Stop at 15 patients (the maximum). The value of 11 toxicities in 15 patients is essentially a placeholder.

Table 5 shows the calculations involved in generating this representation, but for all possible toxicity data. The cells corresponding to data indicating that the trial should continue are colored blue, while the cells corresponding to data indicating that the trial should stop are colored red. The cells corresponding to the boundary points reported by Multc Lean Desktop v. 1.2 are outlined. One can think of the conduct of a trial as moving from cell to cell as additional patients are accrued. If so, then accruing an additional patient with a toxicity is equivalent to moving one cell diagonally down and to the right. Accruing an additional patient with no toxicity is equivalent to moving one cell directly to the right. Thinking about this, it is easy to see that the only places where a trial can move from continuing (a blue cell) to stopping (a red cell) before the maximum number of patients have been accrued are exactly the same as the outlined cells. So it is easy to see that this representation shows the circumstances under which the trial can stop.

Table 5: Multc Lean Desktop Toxicity Stopping Calculations with v. 1.2 Boundary

		Patients														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Toxicities	0	0/1: .2501	0/2: .1252	0/3: .0627	0/4: .0314	0/5: .0157	0/6: .0079	0/7: .0040	0/8: .0020	0/9: .0010	0/10: .0005	0/11: .0003	0/12: .0001	0/13: .0001	0/14: .0000	0/15: .0000
	1	1/1: .7499	1/2: .5000	1/3: .3127	1/4: .1878	1/5: .1097	1/6: .0628	1/7: .0354	1/8: .0197	1/9: .0109	1/10: .0060	1/11: .0032	1/12: .0018	1/13: .0009	1/14: .0005	1/15: .0003
	2	NA	2/2: .8748	2/3: .6873	2/4: .5000	2/5: .3440	2/6: .2270	2/7: .1450	2/8: .0903	2/9: .0551	2/10: .0331	2/11: .0196	2/12: .0114	2/13: .0066	2/14: .0038	2/15: .0022
	3	NA	NA	3/3: .9373	3/4: .8122	3/5: .6560	3/6: .5000	3/7: .3636	3/8: .2544	3/9: .1725	3/10: .1139	3/11: .0736	3/12: .0467	3/13: .0291	3/14: .0179	3/15: .0109
	4	NA	NA	NA	4/4: .9686	4/5: .8903	4/6: .7730	4/7: .6364	4/8: .5000	4/9: .3773	4/10: .2750	4/11: .1946	4/12: .1342	4/13: .0905	4/14: .0599	4/15: .0390
	5	NA	NA	NA	NA	5/5: .9843	5/6: .9372	5/7: .8550	5/8: .7456	5/9: .6227	5/10: .5000	5/11: .3875	5/12: .2912	5/13: .2128	5/14: .1518	5/15: .1060
	6	NA	NA	NA	NA	NA	6/6: .9921	6/7: .9646	6/8: .9097	6/9: .8275	6/10: .7250	6/11: .6125	6/12: .5000	6/13: .3956	6/14: .3043	6/15: .2282
	7	NA	NA	NA	NA	NA	NA	7/7: .9960	7/8: .9803	7/9: .9449	7/10: .8861	7/11: .8054	7/12: .7088	7/13: .6044	7/14: .5000	7/15: .4022
	8	NA	NA	NA	NA	NA	NA	NA	8/8: .9980	8/9: .9891	8/10: .9669	8/11: .9264	8/12: .8658	8/13: .7872	8/14: .6957	8/15: .5978
	9	NA	NA	NA	NA	NA	NA	NA	NA	9/9: .9990	9/10: .9940	9/11: .9804	9/12: .9533	9/13: .9095	9/14: .8482	9/15: .7718
	10	NA	NA	NA	NA	NA	NA	NA	NA	NA	10/10: .9995	10/11: .9968	10/12: .9886	10/13: .9709	10/14: .9401	10/15: .8940
	11	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	11/11: .9997	11/12: .9982	11/13: .9934	11/14: .9821	11/15: .9610
	12	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	12/12: .9999	12/13: .9991	12/14: .9962	12/15: .9891
	13	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	13/13: .9999	13/14: .9995	13/15: .9978
	14	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	14/14: 1.0000	14/15: .9997
	15	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	15/15: 1.0000

Multc Lean Desktop v. 2.0

The following is the v. 2.0 output from Multc Lean Desktop:

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)**
1-3	Never stop with this many patients
4	4
5	5
6-7	6-7
8	7-8
9-10	8-10
11-12	9-12
13	10-13
14	11-14
15	Always stop with this many patients

Again, I hope this table is self-explanatory. Due to the way in which the table is summarized into ranges, some truly impossible conditions are included where there are more toxicities than patients, but we believe this is less confusing than expanding the table simply to avoid those cases.

Table 6 is the same Table 5, but with all the conditions covered in the v. 2.0 table above having a heavy border. You can see that the table covers all the possible stopping conditions – both those in which the stopping rule would be invoked and those for which the number of patients is the maximum.

Table 6: Multc Lean Desktop Toxicity Stopping Calculations with v. 2.0 Boundary

Toxicities	Patients 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
0	0/1: .2501	0/2: .1252	0/3: .0627	0/4: .0314	0/5: .0157	0/6: .0079	0/7: .0040	0/8: .0020	0/9: .0010	0/10: .0005	0/11: .0003	0/12: .0001	0/13: .0001	0/14: .0000	0/15: .0000
1	1/1: .7499	1/2: .5000	1/3: .3127	1/4: .1878	1/5: .1097	1/6: .0628	1/7: .0354	1/8: .0197	1/9: .0109	1/10: .0060	1/11: .0032	1/12: .0018	1/13: .0009	1/14: .0005	1/15: .0003
2	NA	2/2: .8748	2/3: .6873	2/4: .5000	2/5: .3440	2/6: .2270	2/7: .1450	2/8: .0903	2/9: .0551	2/10: .0331	2/11: .0196	2/12: .0114	2/13: .0066	2/14: .0038	2/15: .0022
3	NA	NA	3/3: .9373	3/4: .8122	3/5: .6560	3/6: .5000	3/7: .3636	3/8: .2544	3/9: .1725	3/10: .1139	3/11: .0736	3/12: .0467	3/13: .0291	3/14: .0179	3/15: .0109
4	NA	NA	NA	4/4: .9686	4/5: .8903	4/6: .7730	4/7: .6364	4/8: .5000	4/9: .3773	4/10: .2750	4/11: .1946	4/12: .1342	4/13: .0905	4/14: .0599	4/15: .0390
5	NA	NA	NA	NA	5/5: .9843	5/6: .9372	5/7: .8550	5/8: .7456	5/9: .6227	5/10: .5000	5/11: .3875	5/12: .2912	5/13: .2128	5/14: .1518	5/15: .1060
6	NA	NA	NA	NA	NA	6/6: .9921	6/7: .9646	6/8: .9097	6/9: .8275	6/10: .7250	6/11: .6125	6/12: .5000	6/13: .3956	6/14: .3043	6/15: .2282
7	NA	NA	NA	NA	NA	NA	7/7: .9960	7/8: .9803	7/9: .9449	7/10: .8861	7/11: .8054	7/12: .7088	7/13: .6044	7/14: .5000	7/15: .4022
8	NA	NA	NA	NA	NA	NA	NA	8/8: .9980	8/9: .9891	8/10: .9669	8/11: .9264	8/12: .8658	8/13: .7872	8/14: .6957	8/15: .5978
9	NA	NA	NA	NA	NA	NA	NA	NA	9/9: .9990	9/10: .9940	9/11: .9804	9/12: .9533	9/13: .9095	9/14: .8482	9/15: .7718
10	NA	NA	NA	NA	NA	NA	NA	NA	NA	10/10: .9995	10/11: .9968	10/12: .9886	10/13: .9709	10/14: .9401	10/15: .8940
11	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	11/11: .9997	11/12: .9982	11/13: .9934	11/14: .9821	11/15: .9610
12	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	12/12: .9999	12/13: .9991	12/14: .9962	12/15: .9891
13	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	13/13: .9999	13/14: .9995	13/15: .9978
14	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	14/14: 1.0000	14/15: .9997
15	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	15/15: 1.0000

Comparisons between the Representations

As with the response stopping boundaries, it is our belief that these three different approaches reflect different but complementary representations of the same toxicity stopping boundaries. As before, in the discussion below, general statements about the boundaries are made with the assumption that the trial has a cohort size of one. These statements are not necessarily true for the situation where the cohort size is greater than one.

All three representations describe the same stopping conditions, but our interpretation of the natures of the representations are:

- **Multc99:** The pairs of numbers represent the places in terms of numbers of patients where the stopping boundary in numbers of toxicities increases. Thus at 4 patients the boundary is 4 toxicities, at 5 patients it increases to 5 toxicities, at 6 patients it increases to 6 toxicities, at 8 patients it increases to 7 toxicities, etc. The intent is to describe the boundary as step function in terms of numbers of patients.
- **Multc Lean Desktop v. 1.2:** The pairs of numbers represent the conditions under which the trial can actually stop if it is conducted correctly and it has not stopped previously. Thus it can stop at 4 patients if there are 4 toxicities, it can stop at 7 patients if there are 6 or more toxicities, it can stop at 10 patients if there are 8 or more toxicities, etc. Note that for example if the trial has accrued 5 patients, there must have been fewer than 4 toxicities at 4 patients, and thus there must be fewer than 5 toxicities among the 5 patients, since there could be at most one additional toxicity observed in the additional patient. Although it is not immediately obvious from the Multc Lean Desktop v. 1.2 output, the trial should stop at 5 patients if 5 toxicities are observed out of 5 patients. This is only possible if 4 toxicities were observed out of the first 4 patients, thus the trial should have stopped at 4 patients if it were to stop at 5 patients. Alternatively, if fewer than 4 toxicities were observed out of 4 patients, then there must be fewer than 5 toxicities observed out of 5 patients, and if the trial continues past 4 patients it cannot logically stop at 5 patients. Thus the trial can't logically stop at 5 patients if it has continued past 4 patients and it is conducted properly. Consequently, the Multc Lean Desktop v. 1.2 representation of the stopping boundary does not contain an entry for 5 patients. If the stopping boundary continues to increase by an additional toxicity for each additional patient, as it does for 6 patients (where 6 toxicities would be required for the trial to stop) then the trial cannot stop, since it is not possible to observe more than one additional toxicity in one additional patient. The first opportunity for the trial to stop after continuing past 4 patients is at 7 patients, where the stopping boundary remains at 6 toxicities as it was for 6 patients. Only at this point, where the stopping boundary does not increase with an additional patient, is it possible for a trial which continued past 4 patients (when there must have been fewer than 4 toxicities) to stop, since if there were 3 toxicities out of 4 patients, and 3 more toxicities were observed in the next 3 patients, there would be 6 toxicities in the first 7 patients. Thus this representation has an entry for 7 patients.
- **Multc Lean Desktop v. 2.0:** The table describes all conditions under which the trial should stop, whether or not it is possible for the trial to stop under those conditions if it is conducted

correctly and has not stopped previously. The intent is to make the stopping conditions as clear and explicit as possible, so there is no ambiguity about the conditions under which a trial should stop, particularly for numbers of patients at which the boundary increases by one toxicity for one additional patient and at which it is not possible for the trial to stop if it is conducted correctly and has not stopped previously. Stopping conditions for certain numbers of patients is left implicit in the other representations, and although these stopping conditions can be determined from them, it is not always immediately obvious how to do so, leading to confusion in some cases. Furthermore, the numbers of patients for which the stopping boundary is not explicitly specified differs between the other representations, which can add further confusion.

Discussion

The Multc99 representation only explicitly lists the stopping conditions when the number of toxicities *increases*, which are precisely the situations where it is logically impossible for the trial to stop. The Multc Lean v. 1.2 representation only lists the conditions where it is logically possible to stop, which in the case of toxicities are the places where the stopping boundary *remains constant*. As a consequence, as can be seen above, the Multc99 and the Multc Lean v. 1.2 representations are essentially complementary subsets of the complete stopping boundary, and the differences can look bizarre at first glance. In the case of a toxicity stopping boundary, the numbers of patients at which the boundary remains constant are the same as the numbers of patients at which the trial can stop. Because the number of toxicities cannot increase by more than one with each additional patient as the trial progresses, the only way the trial can stop is if the boundary remains constant, allowing an additional toxicity in an additional patient to take the number of toxicities from below the boundary to the boundary. Thus the Multc99 and the Multc Lean Desktop v. 1.2 toxicity stopping boundary representations are essentially only specified for complementary numbers of patients. The Multc99 representation, since it describes the numbers of patients for which the boundary increases, allows a fairly straightforward reconstruction of the complete stopping boundary. The Multc Lean v. 1.2 representation requires a bit more thought in reconstructing the complete toxicity stopping boundary, but it does state directly the conditions under which the trial can actually stop. In any case, when comparing the Multc99 and Multc Lean Desktop v. 1.2 representations it can be difficult to realize that they represent the same toxicity stopping boundary.

Calculations

As alluded to above, and as can be seen from the values used in the construction of the stopping boundaries, Multc99 Phase IIa and Multc Lean Desktop actually calculate different values in order to determine the stopping boundary. These values are often similar, and intuitively they should be similar, but they are not identical. This can lead to differences in the stopping boundaries which each determines for what are similar but not identical trial specifications.

Multc99 Phase IIa

Multc99 Phase IIa calculates the probability that a realization from the posterior distribution of the experimental rate of an event will be greater than a constant. In other words, it calculates the complementary CDF of the posterior distribution of the experimental rate. It compares this probability to a threshold, which is the lower cutoff value for an efficacy event (response) or the upper cutoff value for an adverse event (toxicity) to determine if the trial should stop when the data in question are observed.

Formally, the Multc99 Phase IIa stopping rules are to stop if:

$$\Pr[\theta_E > p_{Null} | Data] < p_L \text{ (for an efficacy event)}$$

Or

$$\Pr[\theta_E > p_{Null} | Data] > p_U \text{ (for an adverse event)}$$

Where

- p_{Null} is a fixed constant, and
- $\theta_E | Data \sim Beta(a_E + X, b_E + n - X)$

  Where

  - a_E and b_E are the prior parameters for θ_E
  - X is the number of events observed, and
  - n is the number of patients

In our experience, this Phase IIa trial design is the most frequently used part of the Multc99 software, so much so that many people imply a Phase IIa design when they refer to a Multc99 design and a Phase IIa stopping boundary when they refer to a Multc99 stopping boundary.

Multc Lean Desktop

Assuming the delta (or "shift" or "slip" parameter) is zero, Multc Lean Desktop calculates the probability that a realization from the distribution of the standard or historical rate of an event is greater than (in the case of response) or less than (in the case of toxicity) a realization from the posterior distribution of the experimental rate of the event. That is to say that it calculates the probability that one random variable will be greater than (or less than) another random variable. It compares this probability to a

threshold (the upper cutoff value for the event) to determine if the trial should stop when the data in question are observed.

Formally, assuming that delta is zero, and using the same notation as we used for Multc99 Phase IIa above, the stopping rules are to stop if:

$$\Pr[\theta_S > \theta_E | Data] > \pi^* \text{ (for response)}$$

Or

$$\Pr[\theta_S < \theta_E | Data] > \pi_* \text{ (for toxicity)}$$

Where $\theta_S \sim Beta(a_S, b_S)$

Discussion

Although the calculations used by Multc99 Phase IIa and Multc Lean Desktop are formally quite different, one can imagine that if the distribution of the probability of an event with the standard treatment (or the historical distribution) used by Multc Lean Desktop were degenerate, with all of its mass at a constant, the Multc Lean Desktop calculations should produce the same values as the calculations used by Multc99 Phase IIa, if the two constants were the same. This is true, but Multc Lean Desktop does not allow an arbitrarily degenerate Beta distribution to be used for the distribution of the probability of an event under the standard treatment.

In fact, Multc Lean Desktop has a limit of 1000 on the value of each parameter for the Beta distribution of the probability of an event under the standard treatment, or the historical distribution. In many contexts this is a very large limit, and Beta distributions with parameters in this range have a very small variance.

However, even a Beta(1000, 1000) distribution is not degenerate, and it is not the same as a constant at 0.5. In general, the probability that a realization from a Beta(a, b) distribution will be greater than a realization from a Beta(1000, 1000) distribution is not the same as the probability that a Beta(a, b) distribution will be greater than 0.5.

The trial example discussed above was carefully chosen so that the calculations used by Multc99 Phase IIa and the calculations used by Multc Lean Desktop would produce similar enough results that the stopping boundaries they determine will be the same. This was done to allow a clearer comparison of the representations of the stopping boundaries.

In general, however, even when the Beta distribution for the probability of an event used by Multc Lean Desktop has large parameters, the resulting probability calculations will differ from those used by Multc99 Phase IIa. If the Beta parameters used by Multc Lean Desktop are large, the calculated probabilities will be close to those used by Multc99 Phase IIa, but in general they won't be the same.

Formally, in general, and letting μ_S be the mean of the Beta-distributed θ_S,

$$\Pr[\theta_E > \mu_S | Data] \neq \Pr[\theta_E > \theta_S | Data]$$

In both Multc99 Phase IIa and Multc Lean Desktop, the stopping boundaries are determined by considering hypothetical data (a certain number of events in a certain number of patients) and computing the probabilities discussed above, conditional on the hypothetical data. If the computed probability is outside of the allowed range, *by any amount*, then those hypothetical data represent a situation in which the trial should stop.

In particular, if the probabilities calculated by Multc99 Phase IIa and Multc Lean Desktop for the same hypothetical data differ enough that the probability calculated by Multc99 Phase IIa is within the allowed range but the probability calculated by Multc Lean Desktop is outside of the allowed range, even if they differ by a very small amount, then the two applications will reach opposite conclusions about whether a trial should stop if the hypothetical data are encountered.

Thus it is possible that even very small differences in the calculated probabilities can lead to different stopping boundaries being reported by Multc99 Phase IIa and Multc Lean Desktop.

So if you try to design the same trial using Multc99 Phase IIa and Multc Lean Desktop, the difference in the calculation methods can lead to differences in the reported stopping boundaries, even if the Multc Lean Desktop Beta distribution for the probability of an event under the standard treatment has a mean at the value of the constant used by Multc99 Phase IIa, and a very small variance.

The next version of Multc Lean Desktop will have the option to use a constant in place of a Beta distribution for the probability of events under the standard treatment. When that option is used, the stopping boundaries should be the same as those determined by Multc99 Phase IIa.

Conclusions

The differences in how the stopping boundary is reported between Multc99 and Multc Lean Desktop v. 1.2 can lead to confusion, even when the calculated stopping boundary is the same. We hope that the representation of the stopping boundary in Multc Lean Desktop v. 2.0 eliminates any confusion about what exactly the stopping conditions are.

Since the Multc Lean v. 1.2 output of the stopping boundary represents the circumstances under which a properly conducted trial can actually stop, as opposed to a description of the stopping conditions without regard to their potential for actually stopping a trial, we feel that some Multc Lean Desktop users may wish to see this output in addition to the v. 2.0 full set of stopping conditions. For this reason, Multc Lean Desktop now comes with a mechanism for enabling this additional output if it is desired. For details about how to enable it, please see the Multc Lean Desktop v. 2.0 User's Guide.

The differences in the calculations performed by Multc99 Phase IIa and Multc Lean Desktop can lead to differences in the stopping boundary which is calculated. We expect that when Multc Lean Desktop has the option of performing the same calculations as Multc99 Phase IIa, it will be able to generate the same stopping boundaries as Multc99 Phase IIa.