**Interim Analysis and Stopping Rule**

This study focus on investigating the potential stopping rule for the planned clinical trial. The analysis is performed using Monte-Carlo simulation. The following is the sequence of Monte-Carlo simulation.

1. We create two patient groups (Control and Intervention) with equal mortality rate of 30% (0.3). This mortality rate is set based on the generalised information of ARDS patient mortality rate.
2. These cohorts were generated using random numbers ranging from 0 to 1. The numbers less than 0.3 (or 30% mortality) are noted as 1, indicating the patient did not survive. For example, a 1000 patient group, 300 patients did not survived.
3. For intervention group, the mortality rate is increase by a percentage, for example 50%. Thus, the mortality rate for Intervention group ranges from 30% to 50%.
4. From these two patients group, a random sample of patients are selected. For example 10 patients per arm. Thus, patients from two groups can be classified to:

|  |  |  |
| --- | --- | --- |
|  | **Dead** | **Alive** |
| **Control** | 3 | 7 |
| **Intervention** | 8 | 2 |

1. The patients groups were compared using fisher exact test and a p-value is generated.
2. Step 4 to 5 is repeated with different sample sizes. The sample sizes tested are 1, 2, 3, …, 500,
3. Step 4 to 6 is performed with 10000 iterations.
4. Simulation Step 4 to 7 will yield 10000 p-values at each sample sizes, resulting in a 10000 X 500 matrix.
5. Step 4 to 8 is performed with different increase of mortality rate. The increase of mortality rate tested are 1%, 2%, 3%, …, 50%.
6. For each increase of mortality rate, at different sample sizes, the failure to detect a difference is also calculated (False positives). The False positives is calculated as the incidents of:

(Number of Death in Control/ The number of patients in Control + Increase of Mortality rate) >

(Number of Death in Intervention/ The number of patients in Intervention)

1. A p-value of 0.05 is selected threshold and any simulated p-values that is less than the threshold is considered as statistically significant.
2. For each sample size, the number of occurrence with p<0.05 is divided by the number of Monte-Carlo Simulation (10000), and this ratio is the power of the corresponding sample size at that Increase of Mortality rate.
3. A power value is selected, and the smallest sample size that satisfy the power is noted.
4. For each increase of mortality rate, the power and sample size are noted.
5. Step 3 to Step 14 are repeated with different baseline mortality in control group. The baseline mortality tested are 10%, 20%, 30%, 40% and 50%.

**Two-sided versus One-sided Fisherexact test**

Figure below shows the difference mortality rate between group vs the sample sizes. Figure (left) is two-sided test and (Right) is the one-sided test. Each line denotes the power at alpha value of <0.05. The Y-axis is the mortality differences (%) between groups, and X-axis is the sample size per arm. We tested variable sample size range for the reason of patients recruitment rate may vary depending on season. Equally, we can derive the stopping rule mortality difference at any given sample size at an interim analysis.



**The following are case examples of how this figure can be used to determine the stopping rule.**

**For two sided test**

**Example 1**: At power of 0.5, and sample size per arm = 50. The absolute mortality difference is 20%. Thus, if mortality rate is 30% for Control group. The mortality rate for Intervention is 50%. Thus, at sample size 50 per arm, Control group will observed 15 deaths and Intervention group will observed 25 deaths.

**Example 2**: At power of 0.8, at the sample size per arm of 30. The absolute mortality difference is 35%. Thus, if mortality rate is 30% for Control group, the mortality rate for Intervention will be 65%. Thus, at sample size 30 per arm, Control group will observed 10 deaths and Intervention group will observed 19~20 deaths.

**For one sided test**

**Example 3**: At power of 0.8, at the sample size per arm of 100. The absolute mortality difference is 18%. Thus, if mortality rate is 30% for Control group, the mortality rate for Intervention will be 48%. Thus, at sample size 100 per arm, Control group will observed 30 deaths and Intervention group will observed 48 deaths.

**False Positives**

Figures below show the corresponding false positive rate in detecting a difference between groups when there is actually a difference.



For 80% Power two-sided test, a higher absolute difference in mortality rate between groups was found compared to the one-sided test. The failure of detecting a difference between groups for both two and one-sided test is less than 0.5%.



For 50% Power two-sided test, similar finding was observed. A higher absolute difference in mortality rate between groups was found compared to the one-sided test. The failure of detecting a difference between groups for both two one-sided test is less than 3% where as a one sided test had failure rate of less than 4.5%.

**Different Control Group Mortality**

The figure below shows the sample sizes to detect absolute difference in mortality rate for different baseline mortality in control group at power of 80. It was found that the sample sizes to detect a difference if the baseline mortality are lower at 10% and 20%. However, there is relatively no changes if baseline mortality is 30%, 40% or 50%.

For example, at sample size per arm of 100, if control group mortality is 10% (10/100 patient observed did not survived), a 26% mortality in intervention group (26/100) will be significant and powered. If control group mortality is at 20%, intervention mortality of 39% will be significant. Additional 3 deaths difference is needed

For control group of mortality of 30%, 40% and 50% at 100 sample size per arm, the corresponding intervention group mortality is similar at 50%. The 30% mortality rate for control group is used for the interim and stopping rule as the mortality rate is similar cohort in participating hospital.

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**CURE Stopping Rule**

For the CURE randomised controlled trial, the stopping rule is set based the 80% two sided power graph with Control group mortality of 20%. This mortality rate is based on ICU patient data from 2012-2014 that was generated through simulation. If the mortality rate of the intervention group is significantly different to the control group and the numbers of patients allow 80% power, the trial will be terminated. The difference the will need to be observed according to certain group sample sizes is shown in Figure below.

