Covid Platform

Statistical Design Considerations

(4/2/2020)

1 Primary settings

Number of patients = 1000 / arm

prob hospitalization under Null = 0.15

prob hospitalization under Alternative = 0.10

Accrual rate = 100 / week

2 Simulation Results

2.1 Two arms without early stopping

Final inference:

Efficacy decision if , where is the posterior probability of subgroup and is the posterior hospitalization probability of the standard treatment subgroup .

(1) Type I error = 5% with different ratio of standard treatment

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Ratio % | N0 | N1 | Threshold | Type I Error | Power |
| 1-1 | 25 | 500 | 1500 | 0.954 | 0.05 | 0.9018 |
| 2-1 | 30 | 600 | 1400 | 0.9528 | 0.0499 | 0.9285 |
| 3-1 | 35 | 700 | 1300 | 0.9524 | 0.0499 | 0.9446 |
| 4-1 | 40 | 800 | 1200 | 0.9507 | 0.05 | 0.9553 |
| 5-1 | 45 | 900 | 1100 | 0.9494 | 0.0498 | 0.9586 |
| 6-1 | 50 | 1000 | 1000 | 0.9505 | 0.0498 | 0.9596 |
| 1-2 | 25 | 1500 | 500 | 0.9464 | 0.0499 | 0.9047 |
| 2-2 | 30 | 1400 | 600 | 0.9466 | 0.0496 | 0.9299 |
| 3-2 | 35 | 1300 | 700 | 0.9465 | 0.0498 | 0.9479 |
| 4-2 | 40 | 1200 | 800 | 0.9477 | 0.0498 | 0.9548 |
| 5-2 | 45 | 1100 | 900 | 0.9495 | 0.0499 | 0.9586 |
| 6-2 | 50 | 1000 | 1000 | 0.9505 | 0.0498 | 0.9596 |

(2) Family-wise type I error rates for multiple comparisons across arms

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Ratio % | N0 | N1 | 1 Comparison | 2 Comparison | 3 Comparison | 4 Comparison | 5 Comparison | 6 Comparison | 7 Comparison |
| 1-1 | 25 | 500 | 1500 | 0.05 | 0.0777 | 0.0977 | 0.113 | 0.1256 | 0.1366 | 0.1463 |
| 2-1 | 30 | 600 | 1400 | 0.0499 | 0.0804 | 0.1032 | 0.1211 | 0.1362 | 0.1489 | 0.1603 |
| 3-1 | 35 | 700 | 1300 | 0.0499 | 0.0836 | 0.1082 | 0.1274 | 0.1441 | 0.1582 | 0.1708 |
| 4-1 | 40 | 800 | 1200 | 0.05 | 0.0862 | 0.1141 | 0.1366 | 0.1554 | 0.1717 | 0.1861 |
| 5-1 | 45 | 900 | 1100 | 0.0498 | 0.0873 | 0.1162 | 0.1406 | 0.1621 | 0.1805 | 0.1973 |
| 6-1 | 50 | 1000 | 1000 | 0.0498 | 0.0873 | 0.1183 | 0.1442 | 0.1669 | 0.1866 | 0.2039 |
| 1-2 | 25 | 1500 | 500 | 0.0499 | 0.0933 | 0.1325 | 0.1677 | 0.1993 | 0.2287 | 0.2571 |
| 2-2 | 30 | 1400 | 600 | 0.0496 | 0.0928 | 0.1306 | 0.1651 | 0.1956 | 0.2233 | 0.248 |
| 3-2 | 35 | 1300 | 700 | 0.0498 | 0.094 | 0.1295 | 0.1616 | 0.1904 | 0.2167 | 0.24 |
| 4-2 | 40 | 1200 | 800 | 0.0498 | 0.0918 | 0.1268 | 0.1575 | 0.1843 | 0.2086 | 0.2309 |
| 5-2 | 45 | 1100 | 900 | 0.0499 | 0.0891 | 0.1223 | 0.1508 | 0.1758 | 0.1985 | 0.2188 |
| 6-2 | 50 | 1000 | 1000 | 0.0498 | 0.0873 | 0.1183 | 0.1442 | 0.1669 | 0.1866 | 0.2039 |

2.2 Two arms with Predictive Prob early stopping

Interim analysis schedule:

Nmax per arm = 1000 for PP calculation

* 50.50: even accrual of 100 to 1000 per arm with analysis every 200 patients
* 75.25: 75% accrual to control up to 2000 patients, first analysis 150 vs 50 patients, patients accrue 150 and 50 per arm with analysis every 200 patients
* 25.75: 25% accrual to control up to 2000 patients, first analysis 50 vs 150 patients, patients accrue 50 and 150 per arm with analysis every 200 patients

Predictive Probability threshold calibration at **0.9925**

Null: p0 and p1=0.15 hospitalization rate

Alt: p0=0.15 vs p1=0.1

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Allocation** | **Type I error (Null)** | **Power (Alt)** | **Mean Sample Size** | |
| **Null** | **Alt** |
| 50.50 | 0.0504 | 0.961 | 1983 | 1277 |
| 75.25 | 0.0144 | 0.607 | 1982 | 1508 |
| 25.75 | 0.010 | 0.625 | 1990 | 1520 |