Clinical Trials Assignment

Sample size for metastatic pancreatic cancer trial

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Introduction

This report presents the sample size calculations for a clinical trial comparing **FOLFIRINOX** vs. **FOLFIRINOX + drug X** in patients with metastatic pancreatic cancer. The objective is to determine the required sample size to test primary hypotheses related to the efficacy of the new treatment regimen.

The calculations use the **gsDesign** package in R, particularly the functions `nSurv` and `nBinomial`. The assumptions and methodology follow standard statistical approaches for clinical trials.

Study Assumptions

The following assumptions are made: - Randomization ratio of 1:1 for Randomization 1

- α (the overall significance level) is taken equal to 5% (two-sided, unless a non-inferiority test is needed)
- The power of the trial for the differences of interest: at least 80%
- The accrual rate: 20 patients/month on average
- The number of centers: 50
- Budget: potentially available for a trial of up to 400 patients - The total duration of the trial: not exceed 2.5 years.
- The FOLFORINOX group is expected to fare as in the Conroy et al. (2011) trial, i.e.:
    - ORR (objective response rate) = 0.32 - Median progression-free survival (PFS) = 6.4 months
    - Median overall survival (OS) = 11.1 months
    - Incidence of febrile neutropenia (fever due to decreased levels of white blood cells) = 0.054

- The distributions of PFS and OS are exponential for FOLFORINOX and for FOLFORINOX + drug X.

- The addition of drug X to FOLFORINOX is expected to improve the efficacy outcomes as follows:
    - Absolute increase of 0.17 in ORR
    - 30% reduction in PFS hazard rate
    - 35% reduction in OS hazard rate

1. Sample Size Calculation for PFS as Primary Outcome

a. Number of Required Events

```
library(gsDesign)
nEvents(hr=0.70, alpha=0.05, sided = 2, beta=0.2, ratio = 1)
```

```
## [1] 246.7871
```

```
# [1] 246.7871
```

b. Trial Duration for 300 Patients

```
nSurv(lambdaC=-log(.5)/6.4, hr=0.7, sided=2, alpha=0.05, beta=0.2, gamma=20,
R=15, ratio=1)
```

```
## Fixed design, two-arm trial with time-to-event
## outcome (Lachin and Foulkes, 1986).
## Solving for:  Accrual rate
## Hazard ratio                  H1/H0=0.7/1
## Study duration:                   T=18
## Accrual duration:                   12
## Min. end-of-study follow-up: minfup=6
## Expected events (total, H1):        245.8818
## Expected sample size (total):       380.8799
## Accrual rates:
##      Stratum 1
## 0-12     31.74
## Control event rates (H1):
##       Stratum 1
## 0-Inf    0.1083
## Censoring rates:
##       Stratum 1
## 0-Inf         0
## Power:                 100*(1-beta)=80%
## Type I error (1-sided):   100*alpha=5%
## Equal randomization:          ratio=1
```

c. Number of Patients Required for 2-Year Trial Duration

```
nSurv(lambdaC=-log(.5)/6.4, hr=0.7, sided=2, alpha=0.05, beta=0.2, gamma=20,
R=16.8, ratio=1)
```

```
## Fixed design, two-arm trial with time-to-event
## outcome (Lachin and Foulkes, 1986).
## Solving for:  Accrual rate
## Hazard ratio                  H1/H0=0.7/1
## Study duration:                   T=18
## Accrual duration:                   12
## Min. end-of-study follow-up: minfup=6
## Expected events (total, H1):        245.8818
## Expected sample size (total):       380.8799
## Accrual rates:
##      Stratum 1
## 0-12     31.74
## Control event rates (H1):
##       Stratum 1
## 0-Inf    0.1083
## Censoring rates:
##       Stratum 1
## 0-Inf         0
## Power:                 100*(1-beta)=80%
## Type I error (1-sided):   100*alpha=5%
## Equal randomization:          ratio=1
```

2. Sample Size Calculation for OS as Primary Outcome

a. Number of Required Events

```
nEvents(hr=0.65, alpha=0.05, sided = 2, beta=0.2, ratio = 1)
```

```
## [1] 169.1807
```

```
# [1] 169.1807
```

b. Trial Duration for 300 Patients

```
nSurv(lambdaC=-log(.5)/11.1, hr=0.65, sided=2, alpha=0.05, beta=0.2,
gamma=20, R=15, ratio=1)
```

```
## Fixed design, two-arm trial with time-to-event
## outcome (Lachin and Foulkes, 1986).
## Solving for:  Accrual rate
## Hazard ratio                  H1/H0=0.65/1
## Study duration:                   T=18
## Accrual duration:                   12
## Min. end-of-study follow-up: minfup=6
## Expected events (total, H1):        169.1709
```

```
## Expected sample size (total):       377.7499
## Accrual rates:
##      Stratum 1
## 0-12   31.4792
## Control event rates (H1):
##       Stratum 1
## 0-Inf    0.0624
## Censoring rates:
##       Stratum 1
## 0-Inf         0
## Power:                  100*(1-beta)=80%
## Type I error (1-sided):   100*alpha=5%
## Equal randomization:          ratio=1
```

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3. Choosing the Best Primary Outcome

Based on the results:

OS would be the best primary outcome to choose since it is most relevant and requires about the same number of patients (300) for a trial duration of about 2 years. The assumed HR for OS (HR=0.65) is however suspiciously larger than the assumed HR for PFS (HR=0.70), so it might be a good idea to question the assumed HR for OS, or to choose another outcome as the primary endpoint of the trial.

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4. Powering the Trial for all three endpoints of ORR, PFS, and OS.

A Bonferroni correction is applied to control the Type I error rate at 0.05 (two-sided). The sample size is increased to 400 patients, and the trial duration is extended to 27 months.

Bonferroni Correction:

$\alpha 1 = 0.01$ for ORR, $\alpha 2 = 0.023$ for PFS, and $\alpha 3 = 0.017$ for OS, with $\alpha = \alpha 1 + \alpha 2 + \alpha 3 = 0.05$.

a). ORR Sample Size Calculation

```
nBinomial(p1 = 0.32, p2 = 0.49, alpha = 0.01, sided = 2, beta = 0.2, ratio =
1)
```

```
## [1] 386.6352
```

b). PFS Sample Size Calculation

```
nSurv(lambdaC = -log(0.5)/6.4, hr = 0.7, sided = 2, alpha = 0.023, beta =
0.2,
      gamma = 20, R = 20, ratio = 1)
```

```
## Fixed design, two-arm trial with time-to-event
## outcome (Lachin and Foulkes, 1986).
## Solving for:  Accrual rate
## Hazard ratio                  H1/H0=0.7/1
## Study duration:                   T=18
## Accrual duration:                   12
## Min. end-of-study follow-up: minfup=6
## Expected events (total, H1):        303.8123
## Expected sample size (total):       470.6164
## Accrual rates:
##      Stratum 1
## 0-12    39.218
## Control event rates (H1):
##       Stratum 1
## 0-Inf    0.1083
## Censoring rates:
##       Stratum 1
## 0-Inf         0
## Power:                 100*(1-beta)=80%
## Type I error (1-sided):   100*alpha=2.3%
## Equal randomization:          ratio=1
```

c). OS Sample Size Calculation

```
nSurv(lambdaC = -log(0.5)/11.1, hr = 0.65, sided = 2, alpha = 0.017, beta =
0.2,
      gamma = 20, R = 20, ratio = 1)
```

```
## Fixed design, two-arm trial with time-to-event
## outcome (Lachin and Foulkes, 1986).
## Solving for:  Accrual rate
## Hazard ratio                  H1/H0=0.65/1
## Study duration:                   T=18
## Accrual duration:                   12
## Min. end-of-study follow-up: minfup=6
## Expected events (total, H1):        224.3301
## Expected sample size (total):       500.9175
## Accrual rates:
##      Stratum 1
## 0-12   41.7431
## Control event rates (H1):
##       Stratum 1
## 0-Inf    0.0624
## Censoring rates:
##       Stratum 1
## 0-Inf         0
## Power:                 100*(1-beta)=80%
## Type I error (1-sided):   100*alpha=1.7%
## Equal randomization:          ratio=1
```

5. Evaluating Febrile Neutropenia Risk

Drug X may **increase myelotoxicity**, raising the **febrile neutropenia incidence** from **0.054** to **0.108**.
A **non-inferiority (NI) test** is conducted to assess whether this exceeds the tolerable threshold (**0.162**).

Null Hypothesis:

$$H_0: PFN(T) - PFN(C) > 0.108$$

Alternative Hypothesis:

$$H_A: PFN(T) - PFN(C) < 0.108$$

```
nBinomial(p1 = 0.054, p2 = 0.108, delta0 = 0.054 - 3 * 0.054, alpha = 0.05,
          n = 400, sided = 1, scale = "Difference", ratio = 1, outtype = 2)

##    n1  n2     Power
## 1 200 200 0.5953553
```

Output:

```
      n1   n2       Power
1 200 200 0.5953553
```

Power Calculation:

Using the formula:

$$n = \frac{\left(Z_{1-\beta} + Z_{1-\alpha}\right)^2 \cdot \left(p_E(1-p_E) + p_C(1-p_C)\right)}{(\Delta + \delta)^2}$$

$$n = \frac{\left(Z_{1-\beta} + 1.645\right)^2 \cdot (0.892 * 0.108 + 0.946 * 0.054)}{(-0.054 + 0.108)^2}$$

$$n = \frac{200 * (-0.054 + 0.108)^2}{\left((0.892 * 0.108 + 0.946 * 0.054)^{\left(\frac{1}{2}\right)}\right) - 1.645} = 0.344 = Z_{1-\beta}$$

$$1 - \beta = \phi(0.344) = 0.63$$

The **power is approximately 63%**, which is **below the desired 80% threshold**.
Further adjustments may be needed to ensure sufficient power for this endpoint.