Group Randomized Trial Design For Targeted Agent

A Simulation Study

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Background

- A pharmaceutical company has a promising new drug and would like approval from the FDA to start selling the drug
- The drug is a targeted agent, and the study will be run in lung cancer patients with advanced disease
- The drug works better in patients who are biomarker positive rather than biomarker negative, but there is considerable uncertainty about this finding
- The two-arm trial that is being planned is of a standard therapy versus the combination of the standard therapy and the new agent

Background

- Objective: help the pharmaceutical company design this study by running simulations.
- Issues to consider:
  - # countries: 3 or 4
  - Only including biomarker positive or not
  - Drop-out rate: 5% each year
  - Total study length <= 10 years

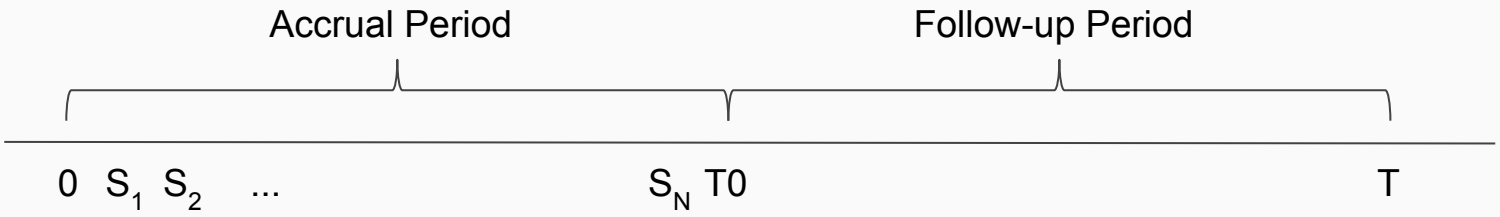
Simulation Structure

- Length of accrual period: T_0
- Length of study: T
- Biomarker status $B_i \sim$ Bernoulli(0.25)
- Group assignment $G_i \sim$ Bernoulli(0.5)
- Rate of accrual $S_i - S_{i-1} \sim$ Exp((# of countries)*72/365)
- Rate of censoring $C_i \sim$ Exp(0.05/365)
- Follow-up Time $T^*_i = \min(X_i, C_i, T)$

Simulation Structure

- Five-year survival probability:
  - Control group: S(5) = 0.3
  - Treatment group:
    - Biomarker +:
      - Uniform case: S(5) ~ Unif(0.35,0.45)
      - Best case: S(5) = 0.45
    - Biomarker -:
      - Uniform case: S(5) ~ Unif(0.3,0.4)
      - Best case: S(5) = 0.4

Simulation Structure

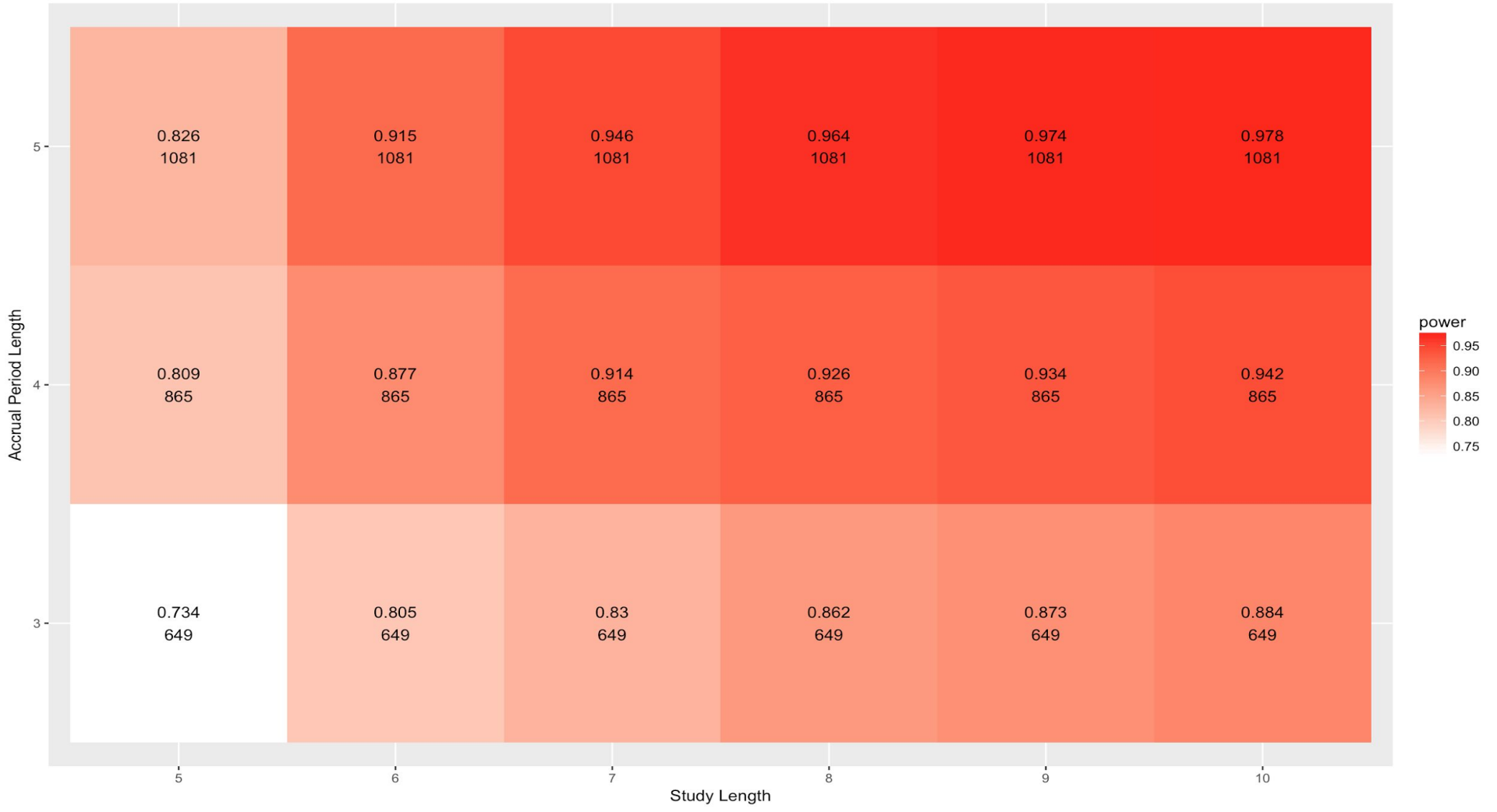


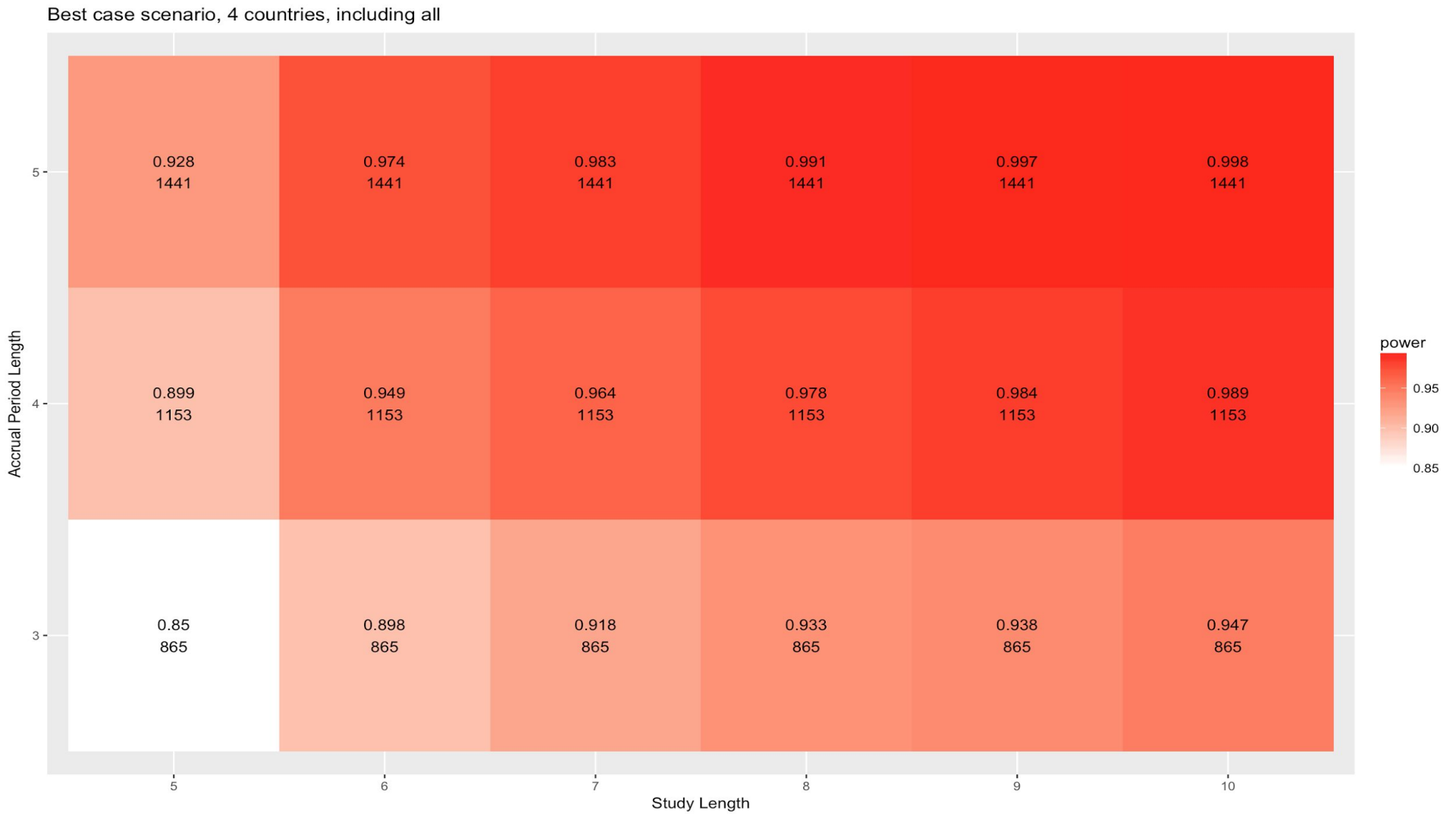
Simulation Structure

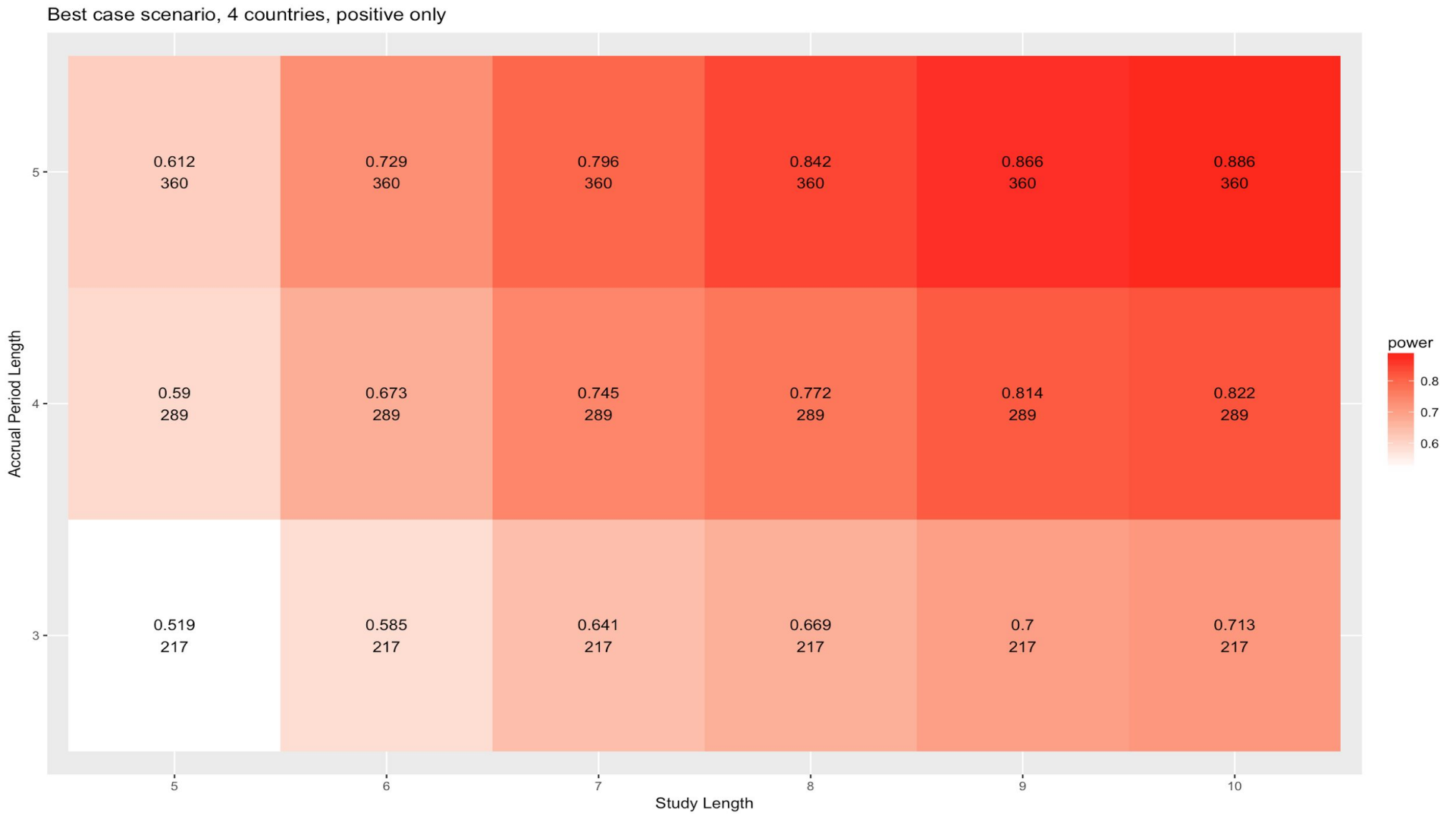
We run 1000 simulations each time with the following options:

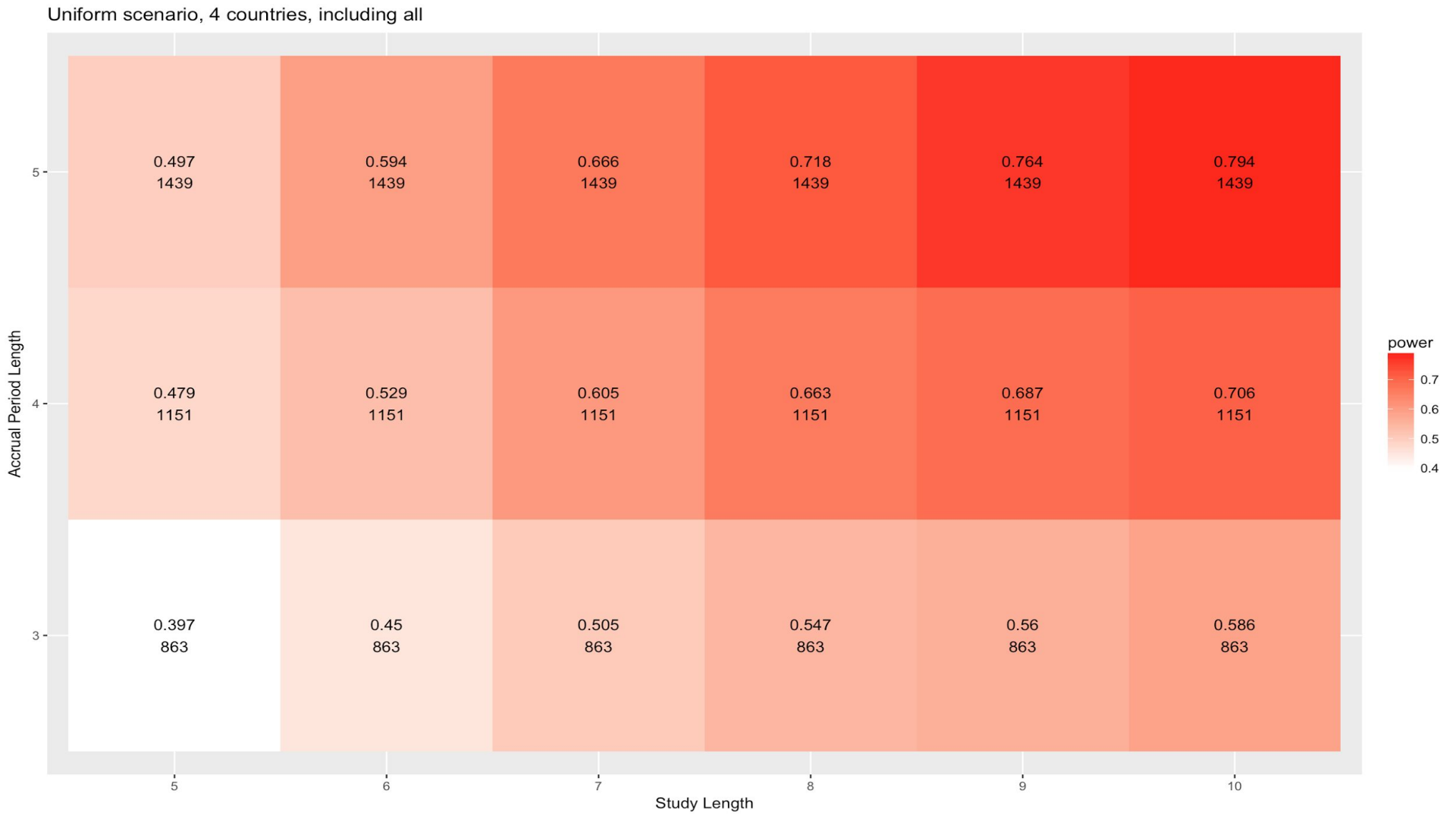
- # countries: {3,4}
- only including biomarker positive patients: {True, False}
- Survival function assumption: {Best case, uniform}
- Accrual time T0 (years): {3,4,5}
- Study total length T (years): {5,6,7,8,9,10}
- Hypothesis test: log-rank test
- Significance criterion: 0.05

Best case scenario, 3 countries, including all




Best case scenario, 4 countries, including all
Accrual Period Length
5
4
3
0.928
1441
0.974
1441
0.983
1441
0.991
1441
0.997
1441
0.998
1441
0.899
1153
0.949
1153
0.964
1153
0.978
1153
0.984
1153
0.989
1153
0.85
865
0.898
865
0.918
865
0.933
865
0.938
865
0.947
865
5
6
7
8
9
10
Study Length
power
0.95
0.90
0.85


Best case scenario, 4 countries, positive only
Accrual Period Length
Study Length
power
0.8
0.7
0.6
5
4
3
5
6
7
8
9
10
0.612
360
0.729
360
0.796
360
0.842
360
0.866
360
0.886
360
0.59
289
0.673
289
0.745
289
0.772
289
0.814
289
0.822
289
0.519
217
0.585
217
0.641
217
0.669
217
0.7
217
0.713
217


Uniform scenario, 4 countries, including all
Accrual Period Length
5
4
3
0.497
1439
0.594
1439
0.666
1439
0.718
1439
0.764
1439
0.794
1439
0.479
1151
0.529
1151
0.605
1151
0.663
1151
0.687
1151
0.706
1151
0.397
863
0.45
863
0.505
863
0.547
863
0.56
863
0.586
863
5
6
7
8
9
10
Study Length
power
0.7
0.6
0.5
0.4

Simulation Results

- Option 1: Shortest length of study
  - T0 = 3, T = 5, Positive_only = False, Countries = 4
  - Sample size = 865, Mean follow-up time = 827 days
  - Power = 0.85
- Option 2: Smallest sample size
  - T0 = 4, T = 9, Positive_only = True, Countries = 4
  - Sample size = 289, Mean follow-up time = 1203 days
  - Power = 0.81
- Option 3: Relatively conservative
  - T0 = 4, T = 7, Positive_only = False, Countries = 3
  - Sample size = 865, Mean follow-up time = 1009 days
  - Power = 0.91

Thanks!

Questions and comments