Multi-center Power Simulation

Teeranan Pokaprakarn; Hiroto Udagawa; Danyi Xiong; Nusrat Rabbee (rabbee@berkeley.edu)

Department of Statistics, University of California, Berkeley, CA

Multi-center Time-dependent Exposure

It is known that treatment effects can vary significantly across sites in multi-center trials. Variability due to a subject's age or disease burden is different than that which arises due to center to center variability. For example, some centers and affiliated physicians are more aggressive in treating the disease under control while some are more conservative and prefer traditional treatment. In this method, we will study several methods for incorporating these center effects into our analysis of survival data. We will build on Glidden and Vittinghoff [1] and investigate their models and scenarios under time-dependent exposure.

A multicenter design is often necessary to provide adequate sample and enhance generalizability of results. If these centers have clustering effects, ignoring them can create wrong and misleading results. Specifically using a simplistic pooled model (ignoring the centers or clusters) lead to under powered studies and to potential biased estimates of treatment effects. In our presentation, we will introduce three different methods of accounting for these center effects: stratified Cox model, fixed effects Cox model, and the random effect frailty model.

- In the stratified Cox model, we take the hazard functions of each center to be unspecified. Thus this lack of structure makes this model the most general. This method essentially throws out all between-center comparisons and model each center based on within-center subjects. Thus as the number of centers increases with a fixed sample size, we lose more information.
- The fixed effects Cox model assumes that the centers act proportionally on a single baseline hazard function. When the number of clusters is small relative to the sample size, this model tends to perform well.
- The frailty model treats the center effects as a sample from a probability distribution. The gamma frailty model assumes that this distribution is gamma with mean 1. The variance determines the between-cluster variability.

We want to explore which method performs well when analyzing multi-center survival data with time-dependent exposure under various scenarios. According to Glidden and Vittinghoff [1], frailty models provides the most flexible, efficient framework for taking into account center effects in most settings.

We will run simulations to compare the performance of our two models with respect to power. We set our = 0.7 for the simulations. We varied our settings based on total sample size (N) and center size.

Example 1: Event rates across centers are equal

In Example 1 we run simulations where the event rates of all the centers (K=40) are equal. This is equivalent to having no center effect whatsoever. The user specifies the parameters by entering a data frame like the following.

```
input_df <- data.frame(cat_id = as.factor(1:40), center.size = rep(10,40),
                       cat_exp.prop = rep(1/3, 40), med.TTE.Control=rep(14,40))
```

Once the parameters for the centers are specified, we can pass this into getpower.multicenter(). To test the different methods, we can specify the 'method' argument of the function. For example, a simulation using a stratified cox model would be specified using the following function call:

cat_id	center.size	cat_exp.prop	med.TTE.Control
1	10.00	0.33	14.00
2	10.00	0.33	14.00
3	10.00	0.33	14.00
.	.	.	.
.	.	.	.
38	10.00	0.33	14.00
39	10.00	0.33	14.00
40	10.00	0.33	14.00

```
getpower.multicenter(nSim = 500, N = 100, beta = 0.7, df = input_df,
                     method="strata", dist=NULL, type = "td",
                     scenario = "strata", maxrelexptime = 1/6, min.futime = 4,
                     min.postexp.futime = 4, output.fn = "output_mult.csv")
```

We ran this simulation with three different methods: independence assumption, strata, and frailty.

We then varied the number of total subjects and the center size which also affects the number of centers in our models. The results of our simulations are shown in the table below.

Method	Center Size	N	Beta	Power
independence	10	100	0.63863	0.380
strata	10	100	0.61980	0.210
frailty	10	100	0.64528	0.378
independence	20	100	0.65104	0.394
strata	20	100	0.65295	0.338
frailty	20	100	0.65816	0.394
independence	10	200	0.64496	0.656
strata	10	200	0.64680	0.474
frailty	10	200	0.65258	0.650
independence	20	200	0.63680	0.642
strata	20	200	0.62627	0.554
frailty	20	200	0.64119	0.644
independence	10	400	0.66143	0.942
strata	10	400	0.64955	0.780
frailty	10	400	0.66669	0.944
independence	20	400	0.65637	0.912
strata	20	400	0.65410	0.826
frailty	20	400	0.65964	0.908

Table 1: Equal Event Rates

Example 2: Events rates across centers are different

Example 2 runs simulations where the median time to event (control group) for each center is specified by the user. For our simple case below (K=3), we create a table like below:

```
input_df <- data.frame(cat_id = as.factor(1:3), center.size = rep(100,3),
                       cat_exp.prop = rep(1/3, 3), med.TTE.Control=c(14,20,31))
```

cat_id	center.size	cat_exp.prop	med.TTE.Control
1	100	0.3333333	14
2	100	0.3333333	20
3	100	0.3333333	31

We run the simulation in the same way we ran example 1 but with our new input data frame.

We do this now with four different methods: marginal cox, fixed effects, stratified, and frailty. Unlike scenario 1, we keep the number of centers fixed at three (K=3) and run four methods:

Method	Center Size	N	Beta	Power
marginal	100	300	0.61398	0.862
fixed effects	100	300	0.65854	0.804
strata	100	300	0.65355	0.792
frailty	100	300	0.64510	0.784

Table 2: Fixed Different Event Rates for 3 Centers

For instances with a small number of centers, we would recommend the strata method. On the other hand, when there are a large number of centers, we would recommend the marginal method.

Example 3: Center effects are gamma distributed

In our final example, we mimic the method described in the Glidden and Vittinghoff [1] paper where we generate data for center effects following the Gamma distribution. We investigate the method using two examples.

In the first we set the same baseline median time to event (control group) for each center. The data frame below shows an N value of 200, a center size of 10 (M=10), number of clusters is 20 (K=20).

```
input_df <- data.frame(cat_id = as.factor(1:20), center.size = rep(10,20),
                       cat_exp.prop = rep(1/3, 20),
                       med.TTE.Control=rep(14,20))
```

cat_id	center.size	cat_exp.prop	med.TTE.Control
1	10.00	0.33	14.00
2	10.00	0.33	14.00
3	10.00	0.33	14.00
.	.	.	.
.	.	.	.
18	10.00	0.33	14.00
19	10.00	0.33	14.00
20	10.00	0.33	14.00

Once the data frame is created, we can pass it into getpower.multicenter(). Like in the previous scenarios, we can specify the 'method' argument of the function for the 'marginal', 'strata', and 'frailty' models. Note, however, that we now add the 'dist = "gamma" ' argument in order to add the random center effect sampled from a gamma distribution.

```
getpower.multicenter(nSim = 500 , N = 100, beta = 0.7, df = input_df,
                     method="strata", dist= "gamma", type = "td",
                     scenario = "strata", maxrelexptime = 1/6, min.futime =4,
                     min.postexp.futime = 4, output.fn = "output_mult.csv")
```

We run this simulation for our 'marginal', 'strata', and 'frailty' methods with varying center sizes, and N values.

Method	Center Size	N	Beta	Power
strata	10	100	0.55675	0.172
frailty	10	100	0.52810	0.228
strata	20	100	0.59069	0.244
frailty	20	100		
strata	10	200	0.62700	0.362
frailty	10	200	0.58137	0.446
strata	20	200	0.66128	0.512
frailty	20	200	0.62095	0.500
strata	10	400	0.64205	0.670
frailty	10	400	0.58194	0.726
strata	20	400	0.65469	0.794
frailty	20	400	0.62063	0.826

Table 3: Gamma Centered Event Rates

In this example, we generated the center effects from a gamma distribution with shape parameter of 2 and scale parameters of 0.5. This distribution has a mean of 1, which will form centers with frailty > 1 and frailty < 1. This simulates our high risk and low risk groups respectively.

The frailty model is recommended over the stratified model in this case since we used gamma frailty to generate the data and center effects.

References

[1] Glidden D, Vittinghoff E. Modelling clustered survival data from multicentre clinical trials. STATISTICS IN MEDICINE 2004;