BIOST 537: Homework 2

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PROBLEM 1.

Consider the following trial data on time until relapse (in months) for patients in remission of acute myelogenous leukemia administered a maintenance chemotherapeutic agent or not:

Maintenance group: 9, 12, 13+, 18, 23, 28+, 31, 34, 45, 45+, 48, 161+.

Control group: 4, 5, 8, 8, 10+, 12, 16+, 23, 27, 30, 38, 43, 45.

(a) Compute the Kaplan-Meier and Nelson-Aalen estimators by filling the following tables for the control and maintenance group.

Table 1: Survival table of remission patients administered maintenance treatment.

Time	At risk (n)	Events (d)	d/n	1-d/n	K-M S(t)	N-A H(t)
9	12	1	0.08	0.92	0.92	0.08
12	11	1	0.09	0.91	0.83	0.17
18	9	1	0.11	0.89	0.74	0.29
23	8	1	0.12	0.88	0.65	0.41
31	6	1	0.17	0.83	0.54	0.58
34	5	1	0.20	0.80	0.43	0.78
45	4	1	0.25	0.75	0.32	1.03
48	2	1	0.50	0.50	0.16	1.53

Table 2: Survival table of remission patients administered a control treatment.

Time	At risk (n)	Events (d)	d/n	1-d/n	K-M S(t)	N-A H(t)
4	13	1	0.08	0.92	0.92	0.08
5	12	1	0.08	0.92	0.85	0.16
8	11	2	0.18	0.82	0.69	0.34
12	8	1	0.12	0.88	0.61	0.47
23	6	1	0.17	0.83	0.50	0.63
27	5	1	0.20	0.80	0.40	0.83
30	4	1	0.25	0.75	0.30	1.08
38	3	1	0.33	0.67	0.20	1.42

Time	At risk (n)	Events (d)	d/n	1-d/n	K-M S(t)	N-A H(t)
43	2	1	0.50	0.50	0.10	1.92
45	1	1	1.00	0.00	0.00	2.92

(b) For each group, what is the estimated probability that no relapse will occur by 36 months?

We fit two nonparametric Kaplan-Meier models of time until relapse for patients in remission of acute myelogenous leukemia, based on whether they were administered a maintenance chemotherapeutic agent or not. Our target is each group's probability of reaching 36 months without relapsing. We estimate this probability to be 0.432 (95% CI: 0.141-0.698) among the maintenance group and 0.303 (95% CI: 0.076-0.574) among the control group.

PROBLEM 2.

In this problem, you will revisit the dataset on methadone maintenance for heroin addicts, as studied in Problem Set 1. Please refer to that homework for a description of the relevant variables.

(a) Plot the Kaplan-Meier estimator of the survival function of the time until exit from maintenance along with pointwise 95% confidence intervals. What is the estimated probability that no exit will occur by one year? Provide a 95% confidence interval for your answer.

See Figure 1. We fit a Kaplan-Meier model of time from entry to exit from methadone maintenance. We estimate the probability of reaching 1 year without exiting is 0.606 (95% CI: 0.538-0.667).

(b) Provide the estimated median time until exit from maintenance and associated 95% confidence interval by:

i. scrutinizing values of the Kaplan-Meier estimator and associated confidence intervals (explain how you obtain your answer);

ii. using the median estimate and confidence intervals provided by the `survfit` command.

The Kaplan-Meier survival function estimates median time until exit from maintenance to be 496 days, approximately 1.4 years (95% CI: 393-546 days). The CI for this median was constructed the set of times in which S(t)=0.5 could be true.

The `survfit` function estimates the median time to be 504 days, approximately 1.4 years (95% CI: 394-550 days).

(c) In this part, you will investigate differences between patients with and without a history of incarceration.

i. On the same graph, plot the Kaplan-Meier estimator of the survival function of the time until exit from maintenance for patients with a history of incarceration and for patient without.

Investigators followed a cohort of 238 individuals with heroin use disorder who entered methadone maintenance programs in either of two clinics in Sydney, Australia over an 18-month period during the late 1980s. The purpose of the study was to identify factors associated to retention in methadone maintenance. Time from entry into the study to exit from methadone maintenance is the duration of interest. More details can be found in Caplehorn and Bell (1991).

See Figure 2. From the 238 individuals enrolled in this study, we fit two non-parametric models of time from entry into the study to exit from methadone maintenance: one for patients from with a history of incarceration and another for patients without a history of incarceration.

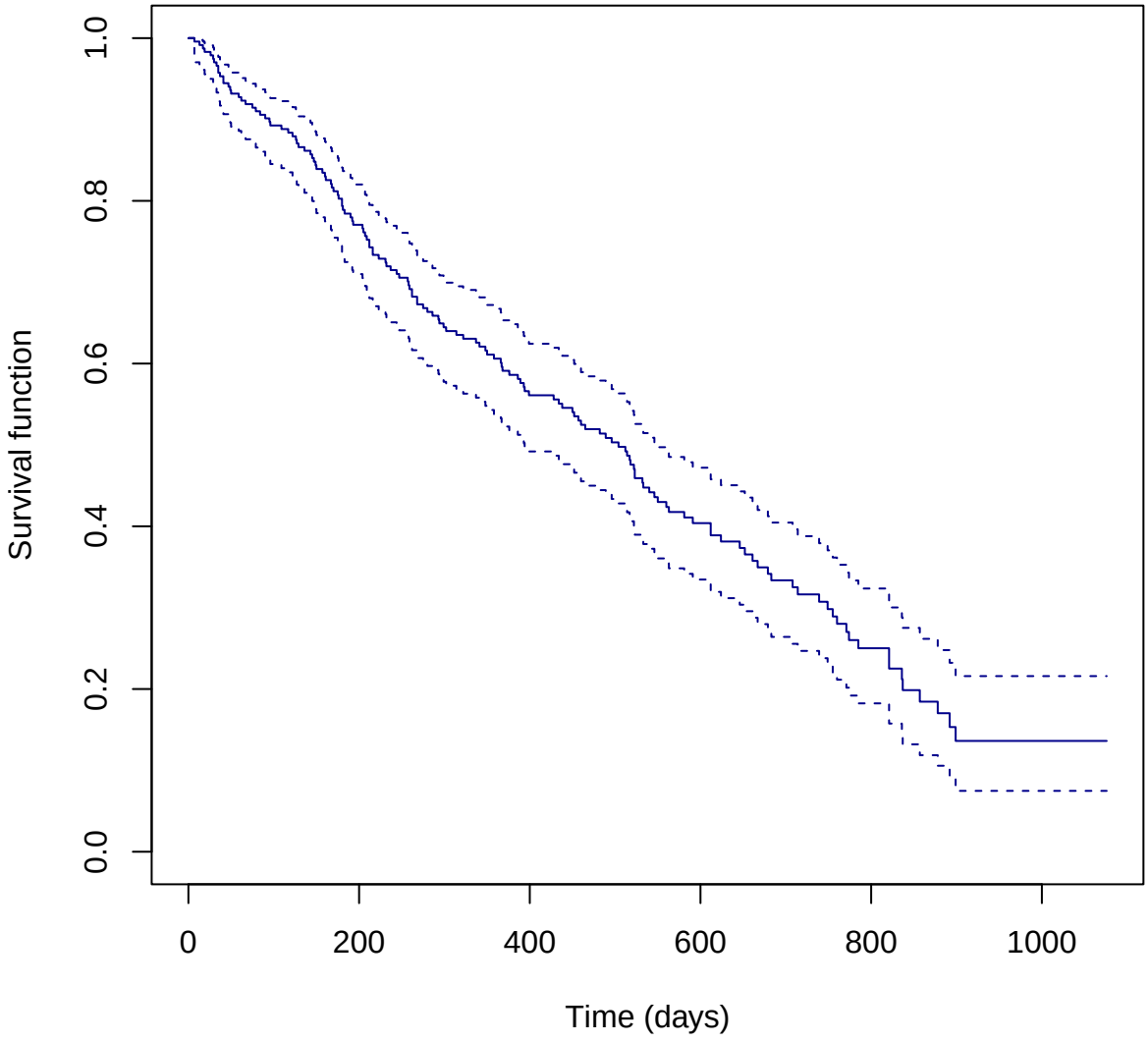

Figure 1: Time from entry to exit from methadone maintenence. Survival is modeled by a nonparametric Kaplan-Meier estimator.

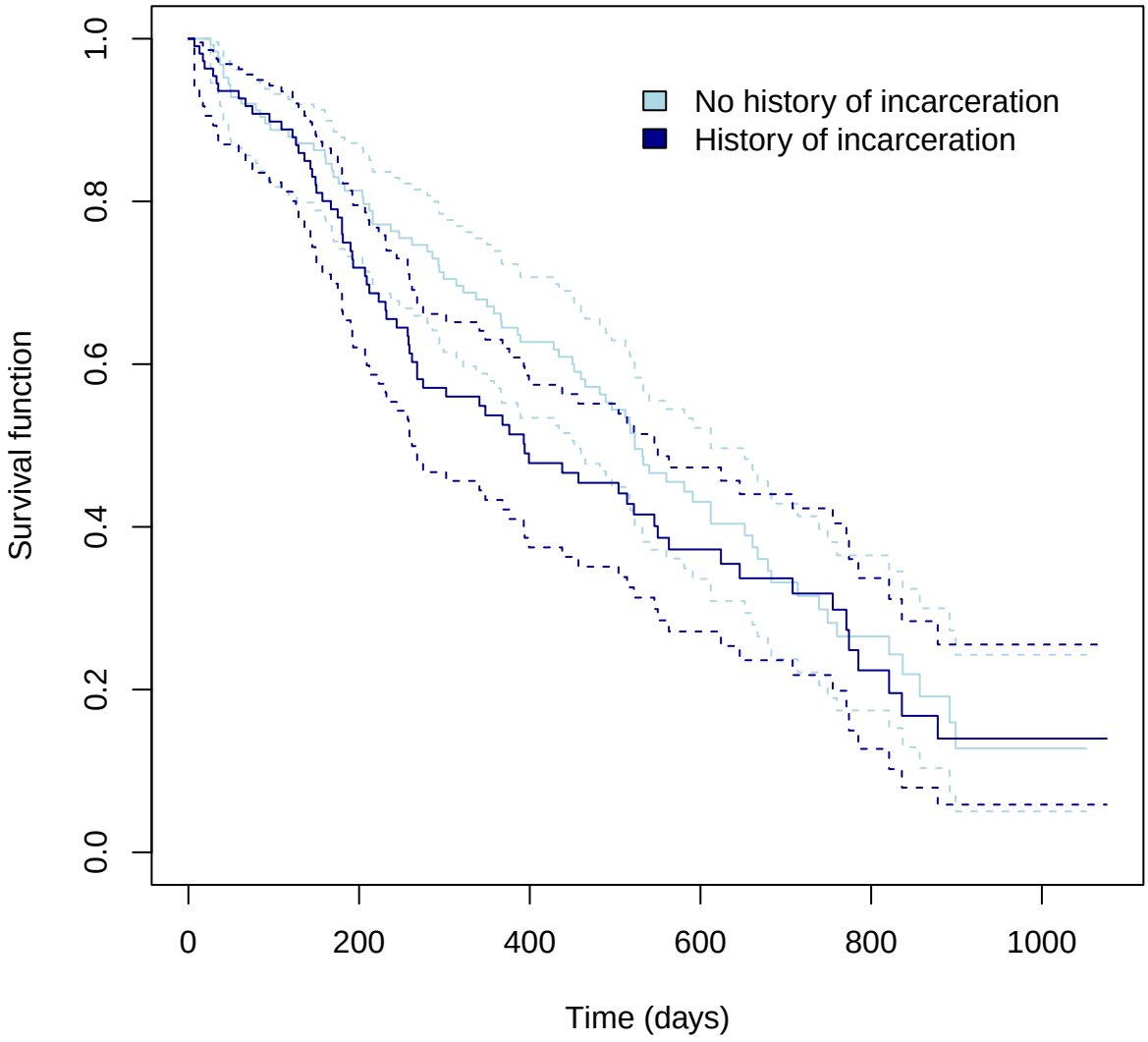

Figure 2: Kaplan-Meier estimator of time until exit from maintenance for patients with and without a history of incarceration.

ii. Does the probability that no exit occurred by 8 months differ significantly between these two groups?

A Wald's test using Greenwood's estimation of standard error determined there is insufficient evidence in our sample the probability of lasting 8 months without exit is statistically different between patients with and without a history of incarceration, at $\alpha = 5\%$ (p=0.077)

iii. Based on the log-rank test, does the distribution of time until exit from maintenance differ significantly by history of incarceration?

A log-rank test determined there is insufficient evidence in our sample that time from entry into the study to exit from methadone maintenance differs significantly between patients with and without a history of incarceration (p=0.3).

iv. Based on the Wilcoxon-Gehan-Breslow test, does the distribution of time until exit from maintenance differ significantly by history of incarceration?

The Wilcoxon-Gehan-Breslow (WGB) weighted log-rank test, which emphasizes separation between survival curves at earlier study times, makes the same conclusion as the unweighted log-rank test (p=0.1).

v. Plot estimated hazard functions for patients with and without a history of incarceration. Briefly indicate how this plot may inform you regarding the power of the log-rank test as well as expected differences in the magnitude of the chi-square statistics from the logrank and Wilcoxon-Gehan-Breslow tests.

See Figure 3. The log-rank test has the strongest power when the groups it compares have proportional hazard throughout the study period. Overlapping hazard curves indicate our test will have low power. We can expect the weighted WGB test to have a comparatively larger test statistic, due to separate hazard curves around the beginning of the study.

(d) Repeat (c) but substituting history of incarceration by methadone dosage dichotomized at 60mg/day (i.e., compare the subpopulation of patients administered more than 60mg/day of methadone to the subpopulation of patients administered no more than 60 mg/day).

Figure 4 shows survival estimates. Figure 5 shows estimated hazard functions.

A Wald's test using Greenwood's estimation of standard error determined there is insufficient evidence in our sample the probability of lasting 8 months without exit is statistically different for patients with administered methadone dosage higher and lower than 60 m/day ($p<0.001$).

A log-rank test determined there is sufficient evidence in our sample that time from entry into the study to exit from methadone maintenance differs significantly between dosage groups ($p<0.001$). A weighted WGB log-rank test agrees ($p<0.001$).

(e) Based on a stratified log-rank test, does the time until exit from maintenance differ by history of previous incarceration adjusting for clinic membership? State explicitly what the null and alternative hypotheses are and contrast with what they are in a standard log-rank test.

A stratified log-rank test evaluates whether survival differs between dosage groups within clinic 1 or clinic 2. The test's null hypothesis is that they do not differ in either clinic, and the alternative hypothesis is that they differ in at least one clinic. This is distinct from the regular log-rank test we conducted earlier, which assessed overall difference between dosage groups, ignorant of clinic. In this instance, a stratified log-rank test has rejected the null hypothesis ($p<0.001$).

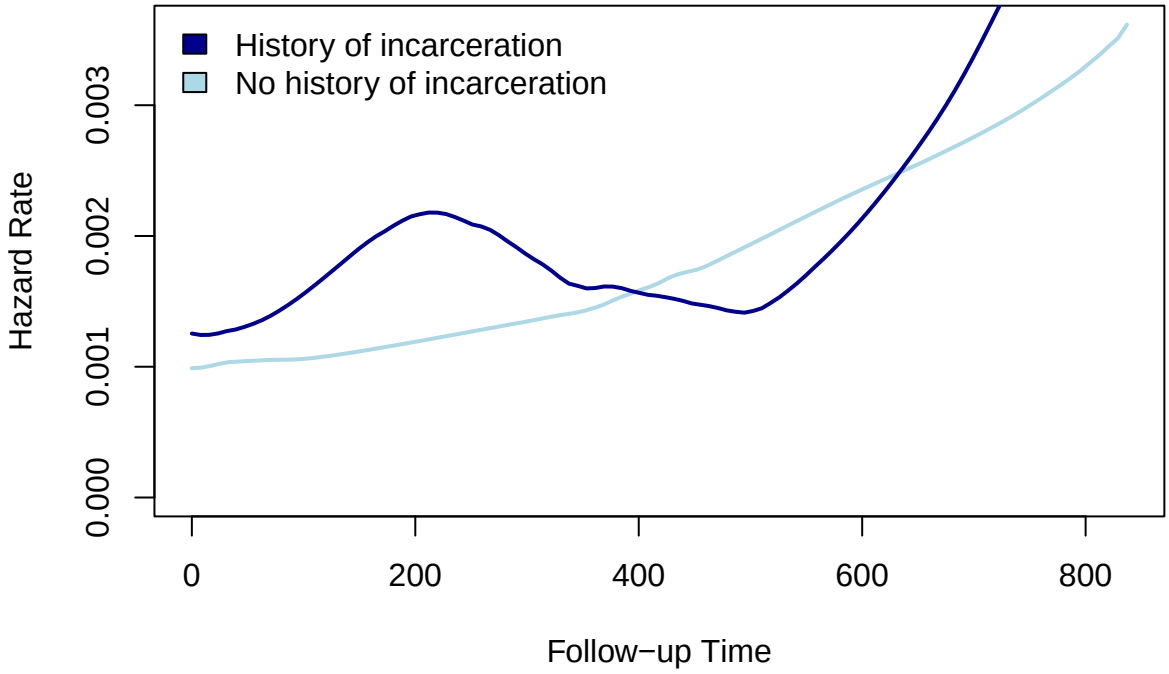

Figure 3: Kernel-based estimator of hazard function (risk of exiting from maintenance in the next instant) for patients with and without a history of incarceration.

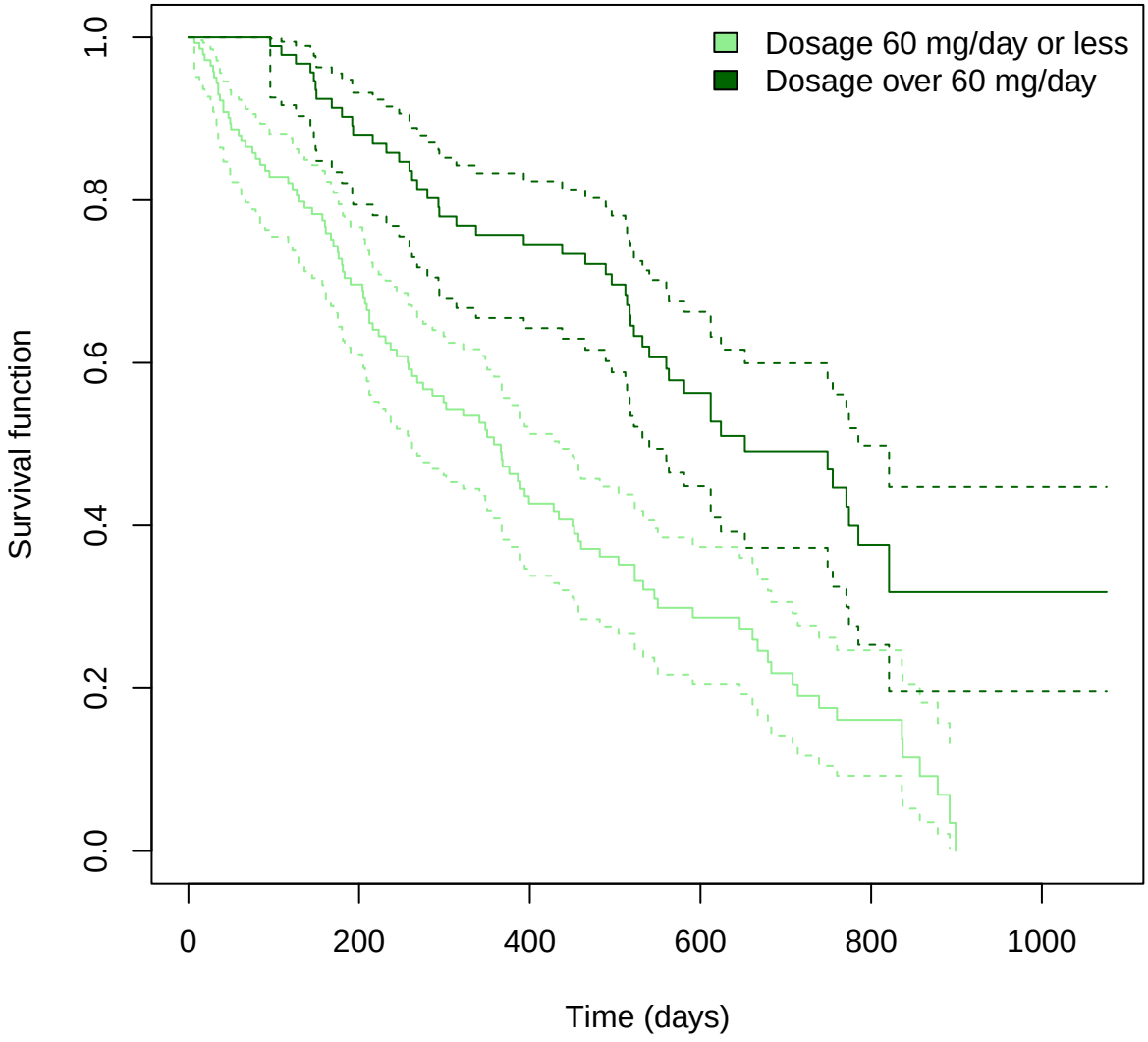

Figure 4: Kaplan-Meier estimator of time until exit from maintenance for patients with administered methadone dosage higher and lower than 60 m/day.

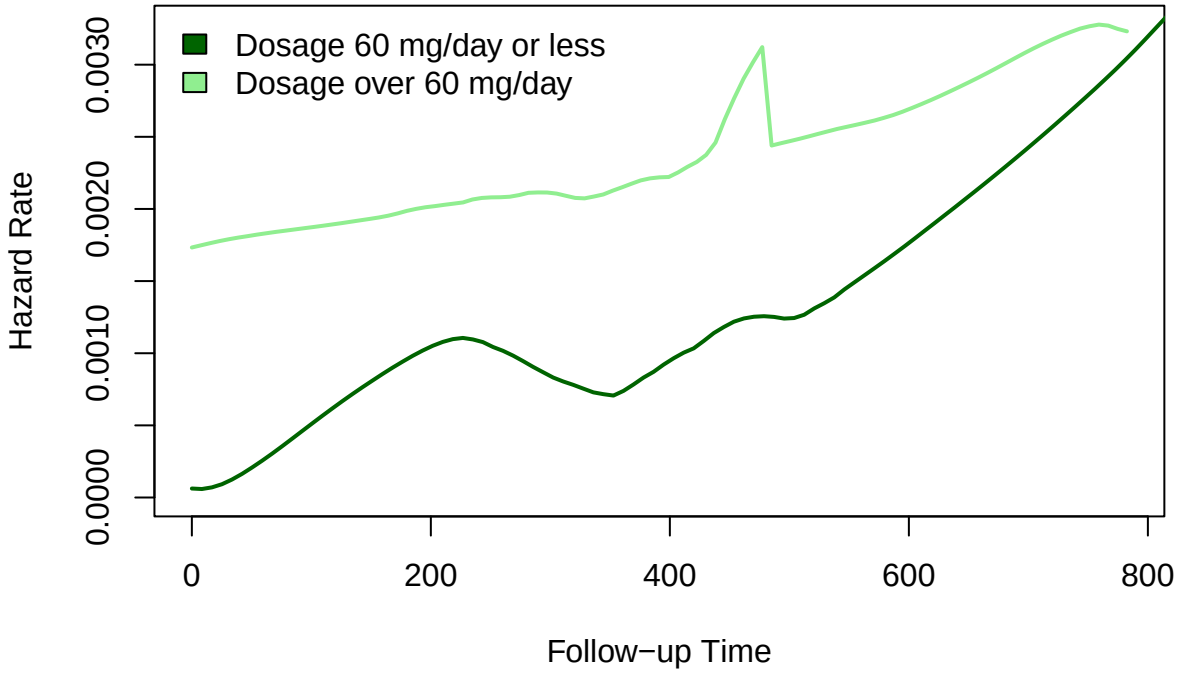

Figure 5: Kernel-based estimator of hazard function (risk of exiting from maintenance in the next instant) for two dosage groups.

(f) What is the estimated median residual time until exit from maintenance at 4, 8 and 12 months? Calculate these estimates using only values of the Kaplan-Meier estimator. Verify your answer using the R function provided for this purpose, and obtain 95% confidence intervals to accompany your estimates.

Using the K-M estimates, we estimate median residual time at the following times to be:

- 4 months (120 days): 248 days
- 8 months (240 days): 256 days
- 12 months (360 days): 183 days

Using the `getmedianres.R` script, we estimate this quantity to be:

- 4 months: 420 days (95% interval*: 376-526)
- 8 months: 427 days (95% interval*: 341-515)
- 12 months: 389 days (95% interval*: 301-461)

*95% interval from 2000 boostrapped resamples

End of report. Code appendix begins on the next page.

Code Appendix

```
# Clear environment
rm(list=ls())

# Setup options
knitr::opts_chunk$set(echo=FALSE, warning=FALSE, message=FALSE, results='hide')
options(knitr.kable.NA = '-', digits = 2)
labs = knitr::all_labels()
labs = labs[!labs %in% c("setup", "allcode")]
# Load relevant packages
library(survival)  # survival model
library(dplyr)     # data manipulation
library(knitr)     # pretty tables
library(ggplot2)   # data visualization
library(muhaz)     # hazard function


# Load data
methadone <- read.csv("../data/methadone.csv")

# Handle missing data

#### Question 1 ####

# Maintenance group survival times
mtnc_surv <- survival::Surv(
  time = c(9,12,13,18,23,28,31,34,45,45,48,161),
  event = c(1,1,0,1,1,0,1,1,1,0,1,0))
# Control group survival times
ctrl_surv <- survival::Surv(
  time = c(4,5,8,8,10,12,16,23,27,30,38,43,45),
  event = c(1,1,1,1,0,1,0,1,1,1,1,1,1))

# Survival table for treated
mtnc_fit <- survival::survfit(mtnc_surv ~ 1, conf.type = "log-log")
mtnc_surv_tab <- data.frame(summary(mtnc_fit)[c(2,3,4,6,8)])
mtnc_surv_tab$"d/n" <- with(mtnc_surv_tab, n.event / n.risk)
mtnc_surv_tab$"1-d/n" <- 1 - mtnc_surv_tab$"d/n"

mtnc_surv_tab[,c(1,2,3,6,7,4,5)] %>%
  knitr::kable(
    col.names = c("Time", "At risk (n)", "Events (d)", "d/n", "1-d/n", "K-M S(t)",
                  "N-A H(t)"),
    caption = "Survival table of remission patients administered maintenance treatment.")

# Survival table for controls
ctrl_fit <- survfit(ctrl_surv ~ 1, conf.type = "log-log")
ctrl_surv_tab <- data.frame(summary(ctrl_fit)[c(2,3,4,6,8)])
ctrl_surv_tab$"d/n" <- with(ctrl_surv_tab, n.event / n.risk)
ctrl_surv_tab$"1-d/n" <- 1 - ctrl_surv_tab$"d/n"

ctrl_surv_tab[,c(1,2,3,6,7,4,5)] %>%
```

```
  kable(
    col.names = c("Time", "At risk (n)", "Events (d)", "d/n", "1-d/n", "K-M S(t)",
                  "N-A H(t)"),
    caption = "Survival table of remission patients administered a control treatment.")

# Maintenance group
summary(mtnc_fit, times = 36)
# Control group
summary(ctrl_fit, times = 36)

#### QUESTION 2 ####

# Plot K-M estimator of survival
meth_surv <- with(methadone, Surv(time, event))
meth_fit <- survfit(meth_surv ~ 1, data = methadone, conf.type = "log-log")
plot(meth_fit, conf.int = TRUE, col = "darkblue",
     ylab = "Survival function", xlab = "Time (days)")

# Estimate survival to one year
# summary(meth_fit, times = 365)

# Median estimate by K-M output
summary(meth_fit, times = c(393, 394, 496, 504, 546, 550))

# Median estimate by survfit()
median(meth_surv) # untransformed CI
quantile(meth_fit, prob = 0.5) # using clog-log

## Plot KM estimator for patients with and without a history of incarceration
meth_fit2 <- survfit(meth_surv ~ prison, conf.type = "log-log", data = methadone)
meth_fit2 %>%
  plot(xlab = "Time (days)", ylab = "Survival function", conf.int = TRUE,
       col = c("lightblue", "darkblue"))
legend(500, 0.97, fill = c("lightblue", "darkblue"), bty = "n",
       legend = c("No history of incarceration","History of incarceration"))

# Compare survival probability at 8 months
temp <- summary(meth_fit2, times = 8*30)
wald_tstat <- abs(diff(temp$surv)) / sqrt(sum(temp$std.err^2))
pval <- 2 * pnorm(wald_tstat, lower.tail = FALSE)
# "If the p is low, the null must go!"
pval < 0.05  # FALSE

# Log-rank test of significance of prison coefficient
survival::survdiff(meth_surv ~ prison, data = methadone)

#WGB test to do a weighted log-rank test
#do this by setting rho = 1 for survdiff
survdiff(meth_surv ~ prison, data = methadone, rho = 1)

# Plot hazard functions, stratified by incarceration history
with(subset(methadone, prison==0), muhaz(time, event)) %>%
  plot(col = "lightblue", lwd = 2)
```

```r
with(subset(methadone, prison==1), muhaz::muhaz(time, event)) %>%
  lines(col = "darkblue", lwd = 2)
legend("topleft", fill = c("darkblue", "lightblue"), bty = "n",
       legend = c("History of incarceration","No history of incarceration"))

# Define binary dosage variable
methadone$dose.bin <- ifelse(methadone$dose > 60, 1, 0)

# Plot KM estimator for patients with dosage above versus below 60 mg/day
fit3 <- survfit(meth_surv ~ dose.bin, conf.type = "log-log", data = methadone)
fit3 %>%
  plot(xlab = "Time (days)", ylab = "Survival function", conf.int = TRUE,
       col = c("lightgreen", "darkgreen"))
legend("topright", fill = c("lightgreen", "darkgreen"), bty = "n",
       legend = c("Dosage 60 mg/day or less", "Dosage over 60 mg/day"))

# Compare survival probability at 8 months
temp2 <- summary(fit3, times = 8*30)
wald_tstat2 <- abs(diff(temp2$surv)) / sqrt(sum(temp2$std.err^2))
pval2 <- 2 * pnorm(wald_tstat2, lower.tail = FALSE)
# "If the p is low, the null must go!"
pval2 < 0.05  # TRUE

# Log-rank test of significance of dosage coefficient
survdiff(meth_surv ~ dose.bin, data = methadone)
# WGB weighed log-rank test
survdiff(meth_surv ~ dose.bin, data = methadone, rho = 1)

# Plot hazard functions, stratified by incarceration history
with(subset(methadone, dose.bin==0), muhaz(time, event)) %>%
  plot(col = "lightgreen", lwd = 2)
with(subset(methadone, dose.bin==1), muhaz::muhaz(time, event)) %>%
  lines(col = "darkgreen", lwd = 2)
legend("topleft", fill = c("darkgreen", "lightgreen"), bty = "n",
       legend = c("Dosage 60 mg/day or less", "Dosage over 60 mg/day"))

# Chi-squared test of dosage group and clinic
table(methadone$dose.bin, methadone$clinic) %>% addmargins %>% chisq.test
# p=0.2 indicates the two are unrelated

# Stratified log-rank test of significance of prison coefficient adjusting for clinic
survdiff(meth_surv ~ dose.bin + strata(clinic), data = methadone)
# p<0.001

## Estimate median residual times
# From K-M estimator
temp3 <- data.frame(time = summary(meth_fit)$time)
temp3$timefrom4mo <- pmax(temp3$time - 4*30, 0)
temp3$timefrom8mo <- pmax(temp3$time - 8*30, 0)
temp3$timefrom12mo <- pmax(temp3$time - 12*30, 0)
# Replace 0 to NA (for later exclusion from median function)
temp3[temp3==0] <- NA
# Estimate median residual times
```

```r
temp3[-1] %>% lapply(median, na.rm = TRUE)

# From provided function
source("../materials/getmedianres.R")
getmedianres(meth_surv, times = c(4*30,8*30,12*30), confint = TRUE)
```

End of document.