The University of Southampton

Academic Year (2014/2015)

Faculty of Social and Human Sciences

Mathematical Sciences

MSc Dissertation

Optimal Design for Survival Experiments – A Simulation Study

Muratcan Tanyerli

Advisor: Dr. Stefanie Biedermann

A dissertation submitted in partial fulfilment of the MSc in Statistics with Applications in Medicine

I am aware of the requirements of good academic practice and the potential penalties for any breaches. I confirm that this dissertation is all my own work.

Executive Summary

Survival experiments consist of analysing longitudinal data on the occurrence of events. Events may include death, injury and onset of illness, recovery from illness or any other meaningful continuous variable. In this study, time-to-event between two treatments or a single treatment with a placebo was used. Time-to-event is the time from entry into a study until a subject has a particular outcome.

Designing of survival experiments is an integral part of the scientific process because resources are always scarce and judicious use of the limited resources is essential. Identifying optimal designs for data collection and assessing their performance in realistic scenarios is therefore paramount. Design of those experiments includes different parameters but one of the most important aspects is how to divide patients into two groups. The balanced design which means assigning the same amount of patients in each group is a commonly used method and is used as a baseline value in this study. A lot of studies are made to find the optimal design in survival experiments but when the data is censored the optimal design changes. However, there is not enough information in the literature on how to deal with censoring. Censoring occurs when patients are lost to follow up or drop out of the study before the study finishes. Also when the study finishes before the patients reach the outcome of interest their data is censored. It is therefore important to find plausible scenarios for different censoring methods and compare optimal designs. This paper uses type-I censoring and random censoring to compare different survival experiment scenarios in order to give a guidance for practitioners planning a survival trial as to what designs would be a good choice.

By looking at the literature, it is seen that c-optimal designs are the best fit for the kind of survival experiments that is used in this study. Other than the c-optimal designs, standardised maximin and locally c-optimal designs are used to compare the c-efficiencies with the balanced designs.

It has been found that whether there was censoring or no censoring, the usage of a c-optimal design increases the efficiency of the parameter estimates. The parameter estimates are the natural logarithm of the baseline hazard and

the coefficient of the covariate which can be either a treatment or a placebo. It has been seen that when the data being analysed had a negative baseline hazard and when a c-optimal design is used rather than a balanced design, the increase in the accuracy of the parameter estimates can go up to 9% for the coefficient of the covariate and it can go up to 21% for the estimate of the natural logarithm of the baseline hazard. This increase in the accuracy reduces when coefficient of the covariate in the data decreases. As this coefficient goes towards 0, the mean squared errors of the parameter estimates decrease but they are still 2% better for the coefficient and 10% better for natural logarithm of the baseline hazard compared to the balanced design. The reason for the change in the accuracy of the mean squared error of the estimates can be explained with the fact that c-optimal design uses different weights to assign patients in each treatment. C-optimal designs tend to assign less patients to support point 0, meaning they are not taking any treatment and in the placebo group when the coefficient is negative, whereas when the coefficient is positive more patients are assigned to support point 0. When this coefficient gets smaller, c-optimal design tends to have a similar patient distribution as the balanced design. If the data is heavily censored, the number of patients assigned to support point 0 increases compared with the low censoring cases. With the increase of proportion of censoring the design assigns more patients where it is more difficult to estimate.

The calculations are made using a baseline hazard very close to zero meaning that the baseline hazard does not have as much effect as the coefficient of the covariate. The reason behind this is that it is a realistic scenario in practice as in (Freireich, et al., 1963). Same calculations can also be made with a positive baseline hazard to see the changes. Also another software instead of R can be used, to get better results for different distributions because when there is heavy censoring R cannot seem to converge in hazard coefficients and this results in some wrong values.

Acknowledgements Page

I would like to express my sincere gratitude to my master thesis advisor Dr. Stefanie Biedermann. Without the support and guidance she has given me, this dissertation would not have been possible.

I want to thank my family Hülya Tanyerli, Hakan Tanyerli, Lale Güler, Ulaş Gürsoy, Emir Uşan and Çağdaş Savaşır for all the emotional and mental support they have given me since the beginning of my life and with their helps in my dissertation.

Contents

Table of Figures

Summary

Censoring is very common in many time-to-event data so it must be addressed carefully. There is not enough literature for optimal design of time-to-event data with censoring. C-optimal designs are found best fit for the type of data that is being used in the study. For that reason, c-optimal designs are used to compare with balanced designs. Three different models are fitted in order to compare the effect of different distributions. Type-I censoring and random censoring is used with different proportions to comprehend effects of different censoring methods. Locally c-optimal designs and standardised maximin designs are found and c-efficiencies are used to compare c-optimal designs with balanced designs.

1. Introduction

Survival experiments have been mostly used in medical studies but also in electronics, engineering and insurance. “Survival analysis is the phrase used to describe the analysis of data in the form of times from a well-defined time origin until the occurrence of some particular event or end-point” (Collett, 2014). As seen in our survival analysis lectures by Alan Kimber, survival analysis methods are usually applied to time but in some cases quantities can be used. The data used in survival experiments are times from an origin until some end-point or event, such data is called survival data or time-to-event data. In general time-to-event data is non-negative and usually continuous. Time-to-event data can arise via a designed experiment or from an observational study. Survival data is special in two main ways, one of them is that data can often be highly skewed and non-normal. “The survival data is not symmetrically distributed, a histogram constructed from the survival times of a group of similar individuals will tend to be positively skewed” (Collett, 2014). This suggests that standard normal distribution methods may not be suitable and new methods should be used to summarise survival data. Second one is that survival times are frequently censored. “The survival time of an individual is said to be censored when the end-point of interest has not been observed for that individual. This may be because the data from a study are to be analysed at a point in time when some individuals are still alive” (Collett, 2014). In a survival study patients can be recruited at same time but they are most of the time not recruited at exactly the same time. “After recruitment, patients are followed up until they die, or until a point in time. Some patients may be lost to follow-up, while others will still be alive at the end of the study” (Collett, 2014).

Designing experiments is an indispensable part of the scientific process because it helps optimizing time and minimizing costs. Resources of the designs are always limited and cautious use of those resources is essential. Therefore identifying optimal designs for data collection and assessing their performance in realistic scenarios is paramount. In this project some logical scenarios will be implemented for a simulation study to compare the performance of several designs for each respective scenario. C-optimal designs for time-to-event data with exponential and Weibull distribution will be implemented. The general aim is to give some general guidance to practitioners planning survival trials to show which designs would be a good choice.

There is little guidance on designs for models with potentially censored data. (Konstantinou, Biedermann, & Kimber, 2015) and (Konstantinou, Biedermann, & Kimber, 2014) found optimal designs for both parametric and semiparametric survival models, and discovered that some optimal designs for parametric models are highly efficient for the semiparametric Cox model while being much easier to find than optimal designs for the Cox model.

The aims of this project are to compare c-optimal designs with the balanced design through simulation and to establish if c-optimal designs for the exponential regression model are also efficient for the estimation in other models.

This dissertation is organised in 5 different sections. In Section 2, time-to-event data, the optimal design and related literature review will be briefly explained. In Section 3, the methodology behind Cox proportional hazards model, accelerated failure time models, corresponding c-optimal designs and proportion of censoring are explained. In Section 4, the results of the study are given in 2 separate sections that consist of balanced designs and c-optimal designs. Section 5 consists of the discussion of the previous results and other recommendations.

2. Background

Let $T_1, \ldots, T_n$ be the time-to-event of patients 1 to n and $t_1, \ldots, t_n$ the corresponding observed values. T is assumed to be a continuous positive random variable. As seen in the lectures of survival analysis by Alan Kimber, the distribution function of T is denoted by $F(t)$, the density function of T is denoted by $f(t)$, the survivor function by $S(t)$ and the hazard function is denoted by $h(t)$

$$F(t) = P(T \leq t)$$

$$f(t) = \lim_{\delta t \to \infty} \left\{ \frac{P(t \leq T < t + \delta t)}{\delta t} \right\} = \frac{dF(t)}{dt}$$

$$S(t) = P(T \geq t) = 1 - F(t)$$

$$h(t) = \lim_{\delta t \to \infty} \left\{ \frac{P(t \leq T < t + \delta t \mid T \geq t)}{\delta t} \right\}. (2.1)$$

The survivor function used in survival analysis summarises the distribution of survival times. If T is a random variable associated with a survival time, the survivor function shows the probability of a randomly selected individual will survive past time t. The hazard function is used to express the risk or hazard of death at some time t, conditional on he or she having survived to that time. According to (Collett, 2014), using the conditional probability given in equation (2.1) a useful relationship between the survivor and hazard functions can be given as

$$h(t) = \lim_{\delta t \to \infty} \left\{ \frac{F(t + \delta t) - F(t)}{\delta t} \right\} \frac{1}{S(t)}.$$

Survival models can be categorised under two types: non-parametric survival models and parametric survival models. Non-parametric survival models are used when no assumptions are needed either about the hazard function or proportional hazards. Kaplan-Meier is a good example of a non-parametric survival model but in our study parametric survival models are going to be used. Parametric survival models let us make more assumptions in order to model the data more precisely.

The parametric models used in this study are: exponential regression and Weibull regression, a semiparametric model was also used, the Cox proportional hazards model. Exponential regression model in its proportional hazards parametrization was used to simulate the required survival data for the study. It has the probability density function $f(t_j, x_j)$, the survivor function $S(t_j, x_j)$ and hazard function $h(x_j)$

$$f(t_j, x_j) = e^{\alpha+\beta x_j} e^{-t_j e^{\alpha+\beta x_j}}, t_j \geq 0$$

$$S(t_j, x_j) = e^{-t_j e^{\alpha+\beta x_j}} , t_j \geq 0$$

$$h(x_j) = e^{\alpha+\beta x_j}$$

Weibull regression model was used in the parameter estimates, also Weibull regression model in its proportional hazards parametrization was used to simulate another survival data. It depends on three parameters α, β, γ and γ also known as the shape parameter is greater than zero.

$$f(t_j, x_j) = e^{\alpha+\beta x_j} \gamma t_j{}^{\gamma-1} e^{-t_j^{\gamma} e^{\alpha+\beta x_j}}, t_j \geq 0$$

$$S(t_j, x_j) = e^{-t_j^{\gamma} e^{\alpha+\beta x_j}} , t_j \geq 0$$

$$h(x_j) = e^{\alpha+\beta x_j} \gamma t_j{}^{\gamma-1}, t_j \geq 0$$

Cox proportional hazards model was also used in the parameter estimates. This model is sometimes preferred instead of the parametric models because there are fewer assumptions to be made. The fitted hazard function for the jth individual is (Cox, 1972)

$$\hat{h}(x_j) = e^{\hat{\beta}' x_j} \hat{h}_0(t),$$

where $\hat{\beta}' x_j$ is the fitted values and $\hat{h}_0(t)$ is the estimated baseline hazard function.

The period of experiment is predetermined with the region $[0, c]$. Let α and β be the unknown model parameters that are going to be used in the study. In survival models with one explanatory variable x_1, e^{α} describes the baseline hazard and β presents how hazard varies with x_1. For the purpose of this study a binary design space is used with $X = \{0,1\}$ which corresponds either to two treatments or a treatment and a placebo.

Two different types of censoring are used in this study. The first one is Type I censoring in which all the patients enter the trial at the same time and their survival times are recorded. If their survival times are greater than the predetermined censoring value represented with a c, the times-to-event gets right censored. This is represented with the following formula: $Y_J = \min\{T_j, c\}$, Y_j being the survival time. The other one is random censoring in which all the patients have randomly distributed entering times into the trial and therefore their censoring times are also random. The distribution used for random censoring is a uniform distribution.

Optimal design is interested in finding the experimental settings that helps us estimate the model parameters of interest most accurately. An approximate design is of the form:

$$\xi = \begin{pmatrix} x_1 & \dots & x_n \\ \omega_1 & \dots & \omega_n \end{pmatrix}, 0 \leq \omega_i \leq 1, \sum_{i=1}^{m} \omega_i = 1$$

The support points $x_i, i = 1, \dots, m,\ m \leq n$ represent the distinct experimental condition, for example $m = 2$ in the binary situation and w_i the corresponding weights represent the proportion of observations in each support point.

For the purpose of this study, two parameter models with Fisher information matrix of the form

$$M(\xi, \alpha, \beta) = \sum_{i=1}^{m} w_i I(x_i, \alpha, \beta) = \sum_{i=1}^{m} \omega_i Q(\theta_i) \begin{pmatrix} 1 & x_i \\ x_i & x_i^2 \end{pmatrix} \quad (2.2)$$

is considered. $I(x_i, \alpha, \beta)$ is the Fisher information at the point x_i and $\theta_i = \alpha + \beta x_i$. From Konstantinou, Biedermann and Kimber (2014), for any real α, $\beta \neq 0$ and any model with the Fisher information matrix (2.2) there exists a c-optimal design for β with exactly two support points. “For the binary design region with a treatment group and a control group the parameter β represents the effect of the treatment on the hazard rate. In dose-response studies the parameter β represents the effect of increasing the dose. Hence we are interested in estimating the effect parameter β as accurately as possible and we treat α as a nuisance parameter" (Schmidt & Schwabe, 2015). "C-optimality is used when the interest is to estimate a function of the parameters, for example one of the parameters. It focuses on estimating a linear combination of the parameters $c'\beta$, where vector c defines the linear combination" (Rivas-Lopez, Lopez-Fidalgo, & Campo, 2014). Therefore from Konstantinou, Biedermann and Kimber (2014), an appropriate optimality criterion is c-optimality for β which minimises the asymptotic variance of the maximum likelihood estimator $\widehat{\beta}$. A design ξ^* is c-optimal for β if the vector $(0\ 1)^T$ is in the range of $M(\xi^*, \alpha, \beta)$ and

$$\xi^* = arg \min_{\xi} M^{-}(\xi, \alpha, \beta) \binom{0}{1},$$

where $M^{-}(\xi, \alpha, \beta)$ is a generalised inverse of the matrix $M(\xi, \alpha, \beta)$.

2.1 Literature Review

In the paper of (Konstantinou, Biedermann, & Kimber, 2014), they focused on optimal designs with potentially censored data since there is not much literature on that subject. It is difficult to find efficient designs for those experiments because the optimal design is dependent on the unknown model parameters. They provide analytical characterisations of locally D- and c-optimal designs. They used the exponential regression model with its natural proportional hazards parametrization and include random and type-I censoring in their research. D- and c-optimal design formulas are explained throughout the paper both for binary experimental condition and an interval design space. β, α and censoring parameters are assumed to be known in the first parts of their paper but those parameters are unknown in practice. According to the paper, e^{α} the baseline hazard for a standard treatment, can often be assumed to be almost known (for design purposes) whereas for β we can often specify a range of plausible values for an improvement with new treatment. To test the robustness of their designs, a real life dataset is used and their results are compared using D-efficiency and c-efficiency. Locally D-optimal and c-optimal designs is used for a vector of parameter values both α and β. It was found that standardised maximin D-optimal design has the highest minimum efficiency but also lower median efficiency. Cluster designs are found to be good alternatives to locally optimal designs both for D-optimal and c-optimal.

(Konstantinou, Biedermann, & Kimber, 2015) used a general expression of the asymptotic covariance matrix of Cox's partial likelihood estimator. They considered cases for only one covariate either binary or a continuous design space with various censoring mechanisms. The reason is that this situation is often encountered in clinical trials where patients are either in different treatments or doses of a treatment. Exponential times-to-event is assumed throughout the paper. First method used is the no censoring case where $c = \infty$, the study is running for as long as necessary. They found that for a positive value of β the optimal weight $1 - \omega$ at point $x_2 = 1$ is the same as the weight ω at point $x_1 = 0$ for the negative β with the same absolute value. Furthermore the efficiencies of the optimal designs compared to the balanced designs are higher when β gets smaller. For Type-I censoring, it has been seen that the optimal design allocates more subjects to the experimental point where the possibility of censoring was greater. Moreover as the proportion of censoring increases the efficiency of the optimal design decreases. This decrease is even more for higher β values. Same results have been found for the random censoring case. The only difference was that the random censoring case was more efficient compared to the Type-I censoring case. In conclusion, they found that optimal designs for partial likelihood estimation and c-optimal designs for the exponential regression model are both similar for heavy censoring. Also, they have found that c-optimal designs are more efficient than the balanced design for estimating β. These comparisons were done through efficiencies and hence are valid for large sample sizes. In this project, the aim is to investigate the performance of c-optimal designs for finite sample sizes through simulation.

3. Methodology

The R software is used to simulate the data with the given exponential and Weibull distributions. The formula $\alpha + \beta x_j$ is used as the corresponding rate to simulate the survival times for exponential distribution and $\frac{-1}{\gamma} * (\alpha + \beta x_j)$ is used as the corresponding rate to simulate survival times for Weibull distribution. 4 different sample sizes are used: 50, 100, 200 and 300. For the baseline value a balanced design was selected which is represented by assigning the same amount of patients in each treatment. This also means that the binary support points x_1 , x_2 have corresponding weights as $\omega_1 = 0.5$, $\omega_2 = 0.5$.

Three types of data are simulated with two different censoring methods. The first one is without censoring so all the patients in the study enter the trial at the same time and their survival times are recorded until the end. The second one is Type I censoring in which the jth individual enters the study at the same time but they have a time limit which is represented with c. The survival times of patients are right censored after some point in time and for our study this is $c = 30$. Any jth individual having a survival time greater than 30 is censored and shown as 30 in the survival data. The third type of data is with random censoring in which the jth individual has a random entry time in the study. Since the entry time is random with a uniform distribution their censoring time is also random.

After simulating the data with exponential proportional hazards and Weibull proportional hazards models, exponential proportional hazards model, Cox proportional hazards model and Weibull proportional hazards model are fitted in order to estimate the model parameters. Cox proportional hazards model just has the β parameter whereas exponential and Weibull proportional hazards model both have α and β parameters. Since α is the baseline hazard it is shown as the intercept of the models and β is the coefficient of the covariate x. As 2 different types of treatments or 1 treatment and 1 placebo is used, the model just has a single covariate and a single β parameter.

The data was analysed through those different models rather than just the exponential model in order to see if the c-optimal designs for the exponential regression can outperform the balanced design even in situation for which they have not been optimised.

The accuracy of the parameter estimates of α and β are examined using Mean Squared Error (MSE) formula:

$$MSE_{\beta} = \frac{1}{n}\sum_{i=1}^{n}\left(\widehat{\beta_{\iota}} - \beta\right)^{2} \quad (3.1)$$

$$MSE_{\alpha} = \frac{1}{n}\sum_{i=1}^{n}(\widehat{\alpha_{\iota}} - \alpha)^{2} \quad (3.2)$$

where n is the sample size, $\widehat{\beta_{\iota}}$ is the parameter estimate of β and $\widehat{\alpha_{\iota}}$ is the parameter estimate of α.

In order to find the optimal design, the corresponding weights should be found. To find the weights of support points x_1^* and x_2^* following c-optimal design is used:

$$\xi^* = \begin{pmatrix} x_1^* & x_2^* \\ \frac{\sqrt{Q(\alpha+\beta x_2^*)}}{\sqrt{Q(\alpha+\beta x_1^*)}+\sqrt{Q(\alpha+\beta x_2^*)}} & \frac{\sqrt{Q(\alpha+\beta x_1^*)}}{\sqrt{Q(\alpha+\beta x_1^*)}+\sqrt{Q(\alpha+\beta x_2^*)}} \end{pmatrix} \quad (3.3)$$

After finding the c-optimal design weights ω_1 and ω_2, those values are taken as the new proportions instead of the balanced design. For example $\omega_1 = 0.45$ and $\omega_2 = 0.55$ with a sample size of 100 represents that 45 of the patients should be assigned to x_1 and 55 of the patients should be assigned to x_2. With those new weights Mean Squared Errors are recalculated and they are compared with the Mean Squared Errors of the balanced design.

For exponential regression $Q(\theta)$ is different for type-I censoring case and random censoring case. (Konstantinou, Biedermann, & Kimber, 2014) found the Fisher information matrix for Type-I censoring at x_i as:

$$I(x_i, \alpha, \beta) = \left(1 - e^{-ce^{\alpha+\beta x_i}}\right)\begin{pmatrix} 1 & x_i \\ x_i & x_i^2 \end{pmatrix}.$$

This yields (2.2) with $Q(\theta) = (1 - e^{-ce^{\theta}})$, so $Q(\alpha + \beta x) = \left(1 - e^{-ce^{\alpha+\beta x}}\right)$.

For random censoring the Fisher information matrix at x_j is:

$$I(x_i,\alpha,\beta) = \left(ce^{\alpha+\beta x_i} + e^{-ce^{\alpha+\beta x_i}} - 1\right)\begin{pmatrix} 1 & x_i \\ x_i & x_i^2 \end{pmatrix}.$$

This yields (2.2) with $Q(\theta) = 1 + (\frac{e^{-ce^{\theta}}-1}{ce^{\theta}})$, so $Q(\alpha+\beta x) = 1 + \left(\frac{e^{-ce^{\alpha+\beta x}}-1}{ce^{\alpha+\beta x}}\right)$.

Also for Weibull regression (Konstantinou, Biedermann, & Kimber, 2014) found the Fisher information matrix for Type-I censoring at x_i as:

$$I(x_i,\alpha,\beta) = \left(1 - e^{-c^{\gamma}e^{\alpha+\beta x_i}}\right)\begin{pmatrix} 1 & x_i \\ x_i & x_i^2 \end{pmatrix}.$$

This yields (2.2) with $Q(\theta) = (1 - e^{-c^{\gamma}e^{\theta}})$, so $Q(\alpha+\beta x) = \left(1 - e^{-c^{\gamma}e^{\alpha+\beta x}}\right)$.

With ω_β being the weight for the balanced design and ω as the weight for the c-optimal design, c-efficiencies are used to compare the c-optimal designs with the balanced designs using the following formula:

$$eff_c(\xi) = \frac{(0\ 1)\ M^{-}\left(\xi_\beta^*,\alpha,\beta\right)\begin{pmatrix}0\\1\end{pmatrix}}{(0\ 1)\ M^{-}(\xi,\alpha,\beta)\begin{pmatrix}0\\1\end{pmatrix}}\ (3.4).$$

Proportion of censoring for each β value and for different types of censoring is found using a simulation model. Survival data is simulated using an exponential distribution and a balanced design with different censoring times. R software is used to find the corresponding percentage values. The percentage of censoring is calculated using the formula:

$$Percentage\ of\ censoring = \frac{Expected\ number\ of\ censored\ observations}{Total\ number\ of\ observations}\ (3.5)$$

Locally c-optimal designs are found using some parameter vectors and c-efficiencies. The parameter vector consists of α and β values such as $\gamma_i = (\alpha_i, \beta_i)$. For the purposes of this study, α values are kept constant and a range of β values are selected to make relevant comparisons. C-efficiencies are calculated using assumed values and true values. With the help of those values a vector of c-efficiencies is calculated for each parameter vector. The parameter vector having the highest minimum efficiency is selected as the best locally c-optimal design. Type-I censoring is assumed throughout this analysis.

After finding the locally c-optimal design, the standardised maximin c-optimal design is found. Let $\beta \in [\beta_0, \beta_1]$, α be fixed and the design space be binary. The standardised maximin c-optimal two point design is

$$\xi^* = \begin{pmatrix} 0 & 1 \\ \omega^* & 1-\omega^* \end{pmatrix},$$

where $\omega^* = \frac{\omega(\beta_0)+\omega(\beta_1)}{2}$ is the optimal weight on zero for the locally c-optimal design and $\omega(\beta_0), \omega(\beta_1)$ are the optimal weights on zero for the locally c-optimal design for β given in (3.3) for β_0 and β_1 respectively.

The optimal support points when the design space $X = [u, v]$ is an interval, is different from the binary case. If $\beta < 0$, the design with support points u and x_2^* , where $x_2^* = v$ is c-optimal. x_2^* is the unique solution of the equation

$$\beta(u - x_2) - 2Q(\alpha + \beta x_2)/Q'(\alpha + \beta x_2)(1 + \frac{\sqrt{Q(\alpha+\beta x_2)}}{\sqrt{Q(\alpha+\beta x_2)}}) = 0 \quad (3.6).$$

4. Results

This chapter explains the results found during the research. They will be presented in 3 different parts. It will start with balanced designs continue with c-optimal designs and end with c-efficiencies. Balanced designs will be evaluated with 3 different types of data: no censored, Type-I censored and random censored. Optimal designs and c-efficiency will be evaluated with 2 different data: Type-I censored and random censored.

In some of the results, a fixed censoring time which is 30 is used and also some comparisons are made using certain proportions of censoring. The censoring time of 30 is selected by looking at the dataset of (Freireich, et al., 1963). In order to select a select plausible parameter estimate, α is taken from the same real life dataset as the censoring time. So α is the maximum likelihood estimate for (Freireich, et al., 1963) dataset which is -2.163. Relevant comparisons are made using 10 different β values. The selected β values are given at Table 1. Only necessary tables are presented below, rest of the tables can be found in Appendix. The β values are selected by taking into consideration two studies made by (Konstantinou, Biedermann, & Kimber, 2014) and (Konstantinou, Biedermann, & Kimber, 2015).

-3.51	-2.30	-1.526	-0.69	-0.10
3.51	2.30	1.526	0.69	0.10

Table 1: Selected β Values

4.1 Balanced Designs

The calculations and tables below show the Mean Squared Error (MSE) using formulas (3.1) and (3.2) for different sample sizes and different β values. The following tables are for balanced designs and they are taken as the baseline values to compare with the optimal designs. Since 3 different models are fitted in the simulation, there are a total of 5 different coefficients to compare. Exponential and Weibull distribution both have α and β whereas Cox PH model only has β. 2 different comparisons are made, the first one is with a common censoring time for each β value and the second one is with a proportion of censoring.

4.1.1 No Censoring

By looking at Table 2 and 3, it can be seen that as the sample size increases the MSE decreases. The decrease in the MSE shows us that the parameter estimates get better as more patients are used.

Parameter estimates with the exponential regression model are the best. Estimates for the Weibull regression model are very close to the exponential regression and the estimates for Cox PH model are the worst. Since the data came from an exponential distribution, it is expected that the corresponding parameter estimates are the best. Also the Weibull model just has one different parameter from the exponential distribution so it is also expected to have close estimates. Cox PH model follows a different distribution compared with the exponential one so it is expected to be the worst.

α	-2.163			
β	-3.51			
Sample Size	**50**	**100**	**200**	**300**
Exponential α	0.040	0.020	0.010	0.007
Exponential β	0.077	0.040	0.020	0.014
Cox PH β	0.362	0.271	0.120	0.069
Weibull α	0.043	0.021	0.010	0.007
Weibull β	0.077	0.040	0.020	0.014

Table 2: MSE for β = -3.51 with No Censoring

α	-2.163			
β	3.51			
Sample Size	**50**	**100**	**200**	**300**
Exponential α	0.041	0.020	0.010	0.007
Exponential β	0.076	0.040	0.020	0.014
Cox PH β	0.380	0.301	0.113	0.073
Weibull α	0.043	0.021	0.010	0.007
Weibull β	0.077	0.040	0.020	0.014

Table 3: MSE for β = 3.51 with No Censoring

When parameter estimates for exponential and Weibull distribution are observed, it can be seen that their MSEs tend to be the same for the negative β value and the positive β value having the same absolute value. Also, it can be concluded that for Cox PH model negative β values tend to estimate the parameter better compared with the positive β value having the same absolute value.

α	-2.163			
β	-1.526			
Sample Size	50	100	200	300
Exponential α	0.041	0.020	0.010	0.007
Exponential β	0.079	0.040	0.020	0.014
Cox PH β	0.141	0.070	0.031	0.020
Weibull α	0.044	0.021	0.010	0.007
Weibull β	0.079	0.040	0.020	0.014

Table 5: MSE for β = -1.526 with No Censoring

α	-2.163			
β	1.526			
Sample Size	50	100	200	300
Exponential α	0.041	0.020	0.010	0.007
Exponential β	0.079	0.040	0.020	0.014
Cox PH β	0.150	0.067	0.032	0.021
Weibull α	0.044	0.021	0.010	0.007
Weibull β	0.079	0.040	0.020	0.014

Table 4: MSE for β = 1.526 with No Censoring

As β values move towards 0, the MSEs of the parameter estimates for the exponential and Weibull regression models tend to be the same whereas the MSEs of the parameter estimates for Cox PH model tend to get lower.

α	-2.163			
β	-0.10			
Sample Size	50	100	200	300
Exponential α	0.041	0.020	0.010	0.007
Exponential β	0.079	0.040	0.020	0.014
Cox PH β	0.091	0.043	0.020	0.014
Weibull α	0.044	0.021	0.010	0.007
Weibull β	0.079	0.040	0.020	0.014

Table 6: MSE for β = -0.10 with No Censoring

α	-2.163			
β	0.10			
Sample Size	50	100	200	300
Exponential α	0.041	0.020	0.010	0.007
Exponential β	0.079	0.040	0.020	0.014
Cox PH β	0.091	0.042	0.021	0.014
Weibull α	0.044	0.021	0.010	0.007
Weibull β	0.079	0.040	0.020	0.014

Table 7: MSE for β = 0.10 with No Censoring

4.1.2 Type-I Censoring for Exponential Data

By looking at Table 8 and Table 9, it can be seen that as the sample size increases the MSE decreases. The decrease in the MSE shows us that the parameter estimates get better as more patients are used. The following tables use a fixed censoring time, the comparisons with certain proportions of censoring will be made after those tables.

Parameter estimates with the exponential regression model are the best. Estimates for the Weibull regression model are very close to the exponential regression and the estimates for Cox PH model are the worst.

α	-2.163			
β	-3.51			
Sample Size	**50**	**100**	**200**	**300**
Exponential α	0.042	0.021	0.010	0.007
Exponential β	0.363	0.281	0.138	0.080
Cox PH β	0.367	0.306	0.151	0.085
Weibull α	0.046	0.022	0.011	0.007
Weibull β	0.551	0.364	0.184	0.109

Table 8:MSE for β = -3.51 with Type-I Censoring

α	-2.163			
β	3.51			
Sample Size	**50**	**100**	**200**	**300**
Exponential α	0.043	0.021	0.01	0.007
Exponential β	0.078	0.04	0.02	0.014
Cox PH β	0.38	0.301	0.113	0.073
Weibull α	0.044	0.021	0.01	0.007
Weibull β	0.079	0.04	0.02	0.014

Table 9: MSE for β = 3.51 with Type-I Censoring

When MSEs of parameter estimates for exponential and Weibull distribution are examined, it can be seen that they tend to be the same for the negative β value and the positive β value having the same absolute value. In contrast with the case of no censoring, it can be concluded that for Cox PH model positive β values tend to estimate the parameter better compared with the negative β value having the same absolute value.

α	-2.163			
β	-1.526			
Sample Size	**50**	**100**	**200**	**300**
Exponential α	0.043	0.021	0.010	0.007
Exponential β	0.123	0.060	0.028	0.019
Cox PH β	0.147	0.072	0.033	0.022
Weibull α	0.046	0.022	0.010	0.007
Weibull β	0.136	0.066	0.030	0.022

Table 11: MSE for β = 1.526 with Type-I Censoring

α	-2.163			
β	1.526			
Sample Size	**50**	**100**	**200**	**300**
Exponential α	0.043	0.021	0.01	0.007
Exponential β	0.081	0.04	0.02	0.014
Cox PH β	0.15	0.067	0.032	0.021
Weibull α	0.045	0.021	0.01	0.007
Weibull β	0.082	0.04	0.02	0.014

Table 10: MSE for β = -1.526 with Type-I Censoring

As β values move towards 0, the MSEs of the parameter estimates for the exponential and Weibull regression models tend to be the same whereas the parameter estimates of Cox PH model tend to be better. Further, the parameter estimates for Type-I censoring are worse compared with the no censoring case.

α	**-2.163**			
β	**-0.10**			
Sample Size	**50**	**100**	**200**	**300**
Exponential α	0.043	0.021	0.01	0.007
Exponential β	0.084	0.042	0.02	0.014
Cox PH β	0.091	0.043	0.021	0.014
Weibull α	0.046	0.021	0.01	0.007
Weibull β	0.085	0.042	0.02	0.014

Table 13: MSE for β = -0.10 with Type-I Censoring

α	**-2.163**			
β	**0.10**			
Sample Size	**50**	**100**	**200**	**300**
Exponential α	0.043	0.021	0.010	0.007
Exponential β	0.083	0.042	0.020	0.014
Cox PH β	0.091	0.043	0.021	0.014
Weibull α	0.046	0.021	0.010	0.007
Weibull β	0.085	0.042	0.020	0.014

Table 12: MSE for β = 0.10 with Type-I Censoring

The effect of different proportions of censoring for different β values are is examined. 0.1, 0.3, 0.5 and 0.7 are selected as the comparison proportions. A simulation of exponential data with the output as the equation (3.5) was run multiple times with different censoring times in order to find the selected proportions. Table 14 shows all of the selected censoring times for both balanced designs and optimal designs. As seen on Table 14 the censoring times for type-I censoring and random censoring are similar. It is also seen that there is a certain proportion between censoring times. It can be easily seen that censoring times of $\beta = -2.30$ are nearly 10 times higher compared with $\beta = 2.30$.

		β					
	Censoring	-2.30	-1.526	-0.69	0.69	1.526	2.30
Type-I	0.1	140	64.62	30.517	15.389	14.117	14.09
	0.3	45	24.52	15.021	7.512	5.354	4.52
	0.5	15.7	11.937	8.387	4.206	2.595	1.58
	0.7	6.53	5.536	4.222	2.126	1.205	0.66
Random	0.1	140.61	65.25	31.245	15.915	14.565	14.544
	0.3	45.725	25.16	15.538	8.045	5.857	5.017
	0.5	16.216	12.39	8.882	4.7195	3.1032	2.12
	0.7	7.0206	6.03	4.724	2.6375	1.7316	1.202

Table 14: Censoring Times for Different Proportions of Censoring

α	-2.163			
β	-2.30			
Proportion of Censoring	**0.1**	**0.3**	**0.5**	**0.7**
Exponential α	0.021	0.021	0.025	0.039
Exponential β	0.046	0.075	0.181	0.360
Cox PH β	0.110	0.112	0.185	0.358
Weibull α	0.022	0.022	0.025	0.048
Weibull β	0.047	0.087	0.235	0.508

Table 16: MSE for β = -2.30 with Type-I Censoring

α	-2.163			
β	2.30			
Proportion of Censoring	**0.1**	**0.3**	**0.5**	**0.7**
Exponential α	0.026	0.052	0.147	0.315
Exponential β	0.046	0.073	0.173	0.354
Cox PH β	0.108	0.110	0.175	0.352
Weibull α	0.026	0.057	0.200	0.531
Weibull β	0.047	0.086	0.231	0.500

Table 18: MSE for β = 2.30 with Type-I Censoring

By looking at Table 15 and Table 16, it can be said that as the proportion of censoring increases the parameter estimates get worse. This is expected since an observed survival time gives more information when estimating the parameters compared with a censored time. The MSEs for parameter estimates for α when a negative β value is used, are better compared with the positive β value with the same absolute value. Whereas the MSEs for parameter estimates for β when a positive β value is used, are better compared with the negative β value with the same absolute value. When the proportion of censoring increases, the MSEs for parameter estimates for β using an exponential distribution and Cox proportional hazards model tend to converge to a similar value whereas the Weibull distribution has the worst estimate when the proportion increases. This is caused by an error in the R software. Some of the Weibull values are affected by the fact that the maximum likelihood estimate of the model could not be converged and β may be infinite.

α	-2.163			
β	-1.526			
Proportion of Censoring	**0.1**	**0.3**	**0.5**	**0.7**
Exponential α	0.021	0.022	0.028	0.044
Exponential β	0.046	0.069	0.119	0.253
Cox PH β	0.069	0.077	0.120	0.251
Weibull α	0.022	0.023	0.028	0.059
Weibull β	0.047	0.078	0.145	0.320

Table 15: MSE for β = -1.526 with Type-I Censoring

α	-2.163			
β	1.526			
Proportion of Censoring	**0.1**	**0.3**	**0.5**	**0.7**
Exponential α	0.026	0.045	0.086	0.198
Exponential β	0.046	0.068	0.114	0.243
Cox PH β	0.067	0.075	0.115	0.242
Weibull α	0.026	0.050	0.115	0.331
Weibull β	0.047	0.077	0.140	0.311

Table 17: MSE for β = 1.526 with Type-I Censoring

By looking at Table 17 and Table 18, it can be said that as β goes to 0 the MSEs of the parameter estimates for α gets worse whereas the parameter estimates for β gets better. The more precisely β values are estimated, the accuracy of α values get worse. When the proportion of censoring is low, the best estimates are for exponential and Weibull distribution. When the proportion of censoring increases, the parameter estimates for Weibull distribution are the worst.

α	**-2.163**			
β	**-0.69**			
Proportion of Censoring	**0.1**	**0.3**	**0.5**	**0.7**
Exponential α	0.021	0.025	0.033	0.055
Exponential β	0.046	0.062	0.090	0.164
Cox PH β	0.050	0.063	0.090	0.163
Weibull α	0.022	0.026	0.035	0.081
Weibull β	0.046	0.064	0.096	0.181

Table 19: MSE for β = -0.69 with Type-I Censoring

α	**-2.163**			
β	**0.69**			
Proportion of Censoring	**0.1**	**0.3**	**0.5**	**0.7**
Exponential α	0.025	0.035	0.055	0.107
Exponential β	0.046	0.060	0.089	0.163
Cox PH β	0.050	0.061	0.089	0.161
Weibull α	0.025	0.037	0.069	0.182
Weibull β	0.047	0.063	0.095	0.180

Table 20: MSE for β = 0.69 with Type-I Censoring

As β goes to 0, the MSEs of the parameter estimates for all the distributions tend to be similar but still the estimate for Weibull distribution is the worst.

4.1.3 Type-I Censoring for Weibull Data

In this section and in section 4.2.2, it was intended to investigate if c-optimal designs for the exponential model are still better than the balanced design if the data come from a Weibull model. The following tables are for a survival data of balanced design with Weibull distribution having different shape and scale parameters. The shape parameters are selected as $\gamma(gamma) = 0.9, 1.1\ and\ 2$. The first two values make the Weibull model close to the exponential model whereas the third one makes the model quite different. It should be noted that when these data are analysed trough the incorrect exponential model, the MSE will contain a substantial bias component, whereas in the previous sections the MSE was dominated by the variance.

α	-2.163			
β	-2.30			
γ	0.9			
Proportion of Censoring	0.1	0.3	0.5	0.7
Exponential α	0.102	0.102	0.090	0.078
Exponential β	0.104	0.101	0.186	0.364
Cox PH β	0.107	0.108	0.176	0.355
Weibull α	0.024	0.081	0.088	0.121
Weibull β	0.128	0.181	0.385	0.755

Table 21: MSE for γ=0.9, β=-2.30 with Type-I Censoring

α	-2.163			
β	2.30			
γ	0.9			
Proportion of Censoring	0.1	0.3	0.5	0.7
Exponential α	0.088	0.081	0.158	0.317
Exponential β	0.102	0.099	0.185	0.366
Cox PH β	0.105	0.107	0.176	0.357
Weibull α	0.089	0.134	0.340	0.790
Weibull β	0.127	0.181	0.385	0.750

Table 22: MSE for γ=0.9, β=2.30 with Type-I Censoring

By looking at Table 21 and Table 22, it can be seen that even though the data follows a Weibull distribution because of the shape parameters, MSEs for the exponential parameter estimates are better compared to Weibull distribution. It was expected because by using 0.9 as the shape parameter, the distribution is close to exponential so the estimates are better. As the exponential distribution, α values have lower MSEs for negative β value.

α	-2.163			
β	-2.30			
γ	1.1			
Proportion of Censoring	0.1	0.3	0.5	0.7
Exponential α	0.075	0.074	0.066	0.059
Exponential β	0.068	0.075	0.168	0.353
Cox PH β	0.107	0.108	0.175	0.355
Weibull α	0.059	0.060	0.060	0.076
Weibull β	0.079	0.110	0.218	0.441

Table 24: MSE for γ=1.1, β=-2.30 with Type-I Censoring

α	-2.163			
β	2.30			
γ	1.1			
Proportion of Censoring	0.1	0.3	0.5	0.7
Exponential α	0.064	0.063	0.333	0.241
Exponential β	0.070	0.075	0.355	0.508
Cox PH β	0.105	0.107	0.357	0.510
Weibull α	0.060	0.085	0.453	1.481
Weibull β	0.081	0.112	0.430	0.894

Table 23: MSE for γ=1.1, β=2.30 with Type-I Censoring

Even though the shape parameter was increased, the distribution is still close to exponentail so the MSEs of exponential distribution is smaller compared to the Weibull distribution. But the MSEs of the parameter estimates for Weibull distribution is becoming smaller as the shape parameter increases. Cox PH and exponential disribution have again similar MSE values when proportion of censoring increases.

α	-2.163			
β	-2.30			
γ	2			
Proportion of Censoring	0.1	0.3	0.5	0.7
Exponential α	1.458	1.448	1.182	0.670
Exponential β	1.019	0.411	0.195	0.335
Cox PH β	0.107	0.108	0.175	0.356
Weibull α	1.184	1.184	1.178	1.173
Weibull β	1.324	1.328	1.321	1.353

Table 25: MSE for γ=2, β=-2.30 with Type-I Censoring

α	-2.163			
β	2.30			
γ	2			
Proportion of Censoring	0.1	0.3	0.5	0.7
Exponential α	1.122	0.467	0.158	0.412
Exponential β	1.016	0.411	0.195	0.334
Cox PH β	0.105	0.107	0.176	0.356
Weibull α	1.177	1.178	1.167	1.188
Weibull β	1.328	1.331	1.323	1.337

Table 26: MSE for γ=2, β=2.30 with Type-I Censoring

By looking at Table 25 and Table 26, it can be concluded that as the distribution moves away from exponential by increasing the shape parameter, MSEs of the Weibull parameters are smaller so the estimates are better. The same error in R causes Weibull model to give errors with high censoring values but still as expected the MSEs for lower censoring values are smaller than the exponential distribution. The MSEs for Cox PH model are lower so the estimates are better.

4.1.4 Random Censoring

By looking at Table 27 and Table 28, it can be seen that as the sample size increases the MSE decreases. The decrease in the MSE shows us that the parameter estimates get better as more patients are used. As expected parameter estimates with the exponential regression model are the best. Estimates for the Weibull regression model are very close to the exponential regression and the estimates for Cox PH model are the worst.

α	-2.163			
β	-3.51			
Sample Size	50	100	200	300
Exponential α	0.042	0.021	0.011	0.007
Exponential β	0.370	0.290	0.133	0.088
Cox PH β	0.378	0.319	0.141	0.093
Weibull α	0.044	0.022	0.011	0.007
Weibull β	0.555	0.367	0.177	0.118

Table 28: MSE for β = -3.51 with Random Censoring

α	-2.163			
β	3.51			
Sample Size	50	100	200	300
Exponential α	0.043	0.021	0.011	0.007
Exponential β	0.080	0.040	0.020	0.014
Cox PH β	0.353	0.301	0.114	0.074
Weibull α	0.043	0.022	0.011	0.007
Weibull β	0.081	0.040	0.020	0.014

Table 27: MSE for β = 3.51 with Random Censoring

When parameter estimates for exponential and Weibull distribution are observed, it can be seen that they tend to be the same for the negative β value and the positive β value having the same absolute value. In contrast with the no censoring, it can be concluded that for Cox PH model positive β values tend to estimate the parameter better compared with the negative β value having the same absolute value.

α	-2.163			
β	-1.526			
Sample Size	50	100	200	300
Exponential α	0.044	0.021	0.010	0.007
Exponential β	0.129	0.059	0.029	0.020
Cox PH β	0.160	0.068	0.031	0.023
Weibull α	0.045	0.022	0.011	0.007
Weibull β	0.145	0.065	0.032	0.022

Table 30: MSE for β = -1.526 with Random Censoring

α	-2.163			
β	1.526			
Sample Size	50	100	200	300
Exponential α	0.046	0.021	0.010	0.007
Exponential β	0.084	0.040	0.020	0.015
Cox PH β	0.152	0.059	0.031	0.021
Weibull α	0.048	0.022	0.011	0.008
Weibull β	0.084	0.040	0.020	0.015

Table 29: MSE for β = 1.526 with Random Censoring

As β values move towards 0, the parameter estimates for the exponential and Weibull regression models tend to be the same whereas the parameter estimates of Cox PH model tend to be better. Furthermore, the parameter estimates for random censoring is worse compared with the no censored and Type-I censored data.

α	-2.163			
β	-0.10			
Sample Size	50	100	200	300
Exponential α	0.042	0.022	0.010	0.007
Exponential β	0.080	0.046	0.020	0.014
Cox PH β	0.088	0.048	0.021	0.014
Weibull α	0.043	0.022	0.011	0.007
Weibull β	0.081	0.046	0.020	0.014

Table 31: MSE for β = -0.10 with Random Censoring

α	-2.163			
β	0.10			
Sample Size	50	100	200	300
Exponential α	0.041	0.021	0.010	0.007
Exponential β	0.080	0.042	0.020	0.014
Cox PH β	0.090	0.044	0.021	0.014
Weibull α	0.042	0.021	0.011	0.007
Weibull β	0.081	0.042	0.020	0.014

Table 32: MSE for β = 0.10 with Random Censoring

The effect of different proportions of censoring for different β values is also examined. As before, 0.1. 0.3, 0.5 and 0.7 are selected as comparison proportions.

α	-2.163			
β	-2.30			
Proportion of Censoring	0.1	0.3	0.5	0.7
Exponential α	0.020	0.020	0.024	0.039
Exponential β	0.046	0.073	0.175	0.360
Cox PH β	0.106	0.108	0.177	0.358
Weibull α	0.021	0.022	0.024	0.048
Weibull β	0.046	0.085	0.234	0.509

Table 34: MSE for β = -2.30 with Random Censoring

α	-2.163			
β	2.30			
Proportion of Censoring	0.1	0.3	0.5	0.7
Exponential α	0.025	0.051	0.145	0.308
Exponential β	0.046	0.073	0.170	0.346
Cox PH β	0.106	0.108	0.176	0.346
Weibull α	0.025	0.058	0.199	0.488
Weibull β	0.046	0.087	0.228	0.469

Table 33: MSE for β = 2.30 with Random Censoring

By looking at Table 33 and Table 34, it can be said that as the proportion of censoring increases the parameter estimates get worse. The parameter estimates for α when a negative β value is used, are better compared with the positive β value with the same absolute value. Whereas the parameter estimates for β when a positive β value is used, are better compared with the negative β value with the same absolute value. When the proportion of censoring increases, the MSEs of the parameter estimates for β using an exponential distribution and Cox proportional hazards model tend to converge to a similar value whereas the Weibull distribution has the worst MSEs for the parameter estimates when the proportion increases.

α	-2.163			
β	-1.526			
Proportion of Censoring	0.1	0.3	0.5	0.7
Exponential α	0.020	0.021	0.027	0.044
Exponential β	0.046	0.067	0.115	0.242
Cox PH β	0.066	0.074	0.116	0.240
Weibull α	0.021	0.022	0.028	0.058
Weibull β	0.047	0.076	0.142	0.311

Table 36: MSE for β = -1.526 with Random Censoring

α	-2.163			
β	1.526			
Proportion of Censoring	0.1	0.3	0.5	0.7
Exponential α	0.025	0.045	0.086	0.197
Exponential β	0.046	0.067	0.114	0.242
Cox PH β	0.066	0.074	0.116	0.241
Weibull α	0.025	0.050	0.116	0.332
Weibull β	0.046	0.077	0.142	0.311

Table 35: MSE for β = 1.526 with Random Censoring

By looking at Table 35 and Table 36, it can be said that as β goes to 0 the parameter estimates for α gets worse whereas the parameter estimates for β gets better. The more precisely β values are estimated, the accuracy of α values get worse. When the proportion of censoring is low, the best estimates are for exponential and Weibull distribution. When the proportion of censoring increases, the parameter estimates for Weibull distribution are the worst.

α	-2.163			
β	-0.69			
Proportion of Censoring	0.1	0.3	0.5	0.7
Exponential α	0.021	0.025	0.033	0.055
Exponential β	0.045	0.060	0.088	0.162
Cox PH β	0.049	0.061	0.088	0.161
Weibull α	0.021	0.025	0.035	0.081
Weibull β	0.046	0.062	0.094	0.178

Table 38: MSE for β = -0.69 with Random Censoring

α	-2.163			
β	0.69			
Proportion of Censoring	0.1	0.3	0.5	0.7
Exponential α	0.024	0.035	0.055	0.103
Exponential β	0.045	0.060	0.089	0.158
Cox PH β	0.049	0.061	0.088	0.157
Weibull α	0.024	0.037	0.069	0.179
Weibull β	0.046	0.062	0.095	0.175

Table 37: MSE for β = 0.69 with Random Censoring

As β goes to 0, the MSEs of the parameter estimates for all the distributions tend to be similar but still the estimate for Weibull distribution is the worst.

4.2 C-optimal Designs

The calculations and tables below show the Mean Squared Error (MSE) using formulas (3.2) and (3.3) for different sample sizes and different β values. The following tables are for c-optimal designs and they are compared with the balanced designs in order to see the difference in MSE values. In this chapter, the no-censoring case is not considered since the c-optimal design for this situation is the balanced design. Also after the c-optimal designs, locally c-optimal designs and standardised maximin designs are given. Two different dataset is used, first one is simulated from an exponential distribution and the second one is simulated from a Weibull distribution.

4.2.1 Type-I Censoring for Exponential Data

α	-2.163			
β	-2.30			
Proportion of Censoring	0.1	0.3	0.5	0.7
Exponential α	0.022	0.027	0.041	0.075
Exponential β	0.046	0.071	0.144	0.327
Cox PH β	0.109	0.108	0.149	0.323
Weibull α	0.023	0.029	0.041	0.093
Weibull β	0.047	0.086	0.217	0.566

Table 40: MSE for β = -2.30 Type-I Censoring C-optimal

α	-2.163			
β	2.30			
Proportion of Censoring	0.1	0.3	0.5	0.7
Exponential α	0.025	0.042	0.097	0.243
Exponential β	0.046	0.068	0.135	0.310
Cox PH β	0.105	0.103	0.140	0.307
Weibull α	0.024	0.049	0.166	0.572
Weibull β	0.047	0.083	0.211	0.525

Table 39: MSE for β = 2.30 Type-I Censoring C-optimal

When the optimal designs are used, as expected the parameter estimates for different distributions get better. It should be noted that this is not only the case if the data is analysed using the exponential model but also if the Weibull model or Cox proportional hazards model are used. By looking at Table 39 and Table 40, it can be said that as the proportion of censoring increases the parameter estimates get worse. The MSE of the parameter estimates for α when a negative β value is used, are better compared with the positive β value with the same absolute value. Whereas the parameter estimates for β when a positive β value is used, are better compared with the negative β value with the same absolute value. The MSE of the parameter estimates for β using an exponential distribution and Cox proportional hazards model tend to converge to a similar value whereas the Weibull distribution has the worst MSE of the parameter estimates when the proportion increases. By looking at those results, it can easily be said that they are similar with the results from the balanced design.

α	-2.163			
β	-2.30			
Proportion of Censoring	0.1	0.3	0.5	0.7
Exponential α	-7%	-28%	-62%	-92%
Exponential β	0%	5%	21%	9%
Cox PH β	2%	4%	19%	10%
Weibull α	-7%	-28%	-63%	-93%
Weibull β	0%	1%	8%	-11%
Weight on 0/1	47/53	39/61	31/69	27/73

Table 44: Improvement for β = -2.30 Type-I Censoring C-optimal

α	-2.163			
β	2.30			
Proportion of Censoring	0.1	0.3	0.5	0.7
Exponential α	6%	20%	34%	23%
Exponential β	0%	7%	22%	13%
Cox PH β	3%	6%	20%	13%
Weibull α	6%	15%	17%	-8%
Weibull β	0%	3%	9%	-5%
Weight on 0/1	53/47	61/39	69/31	73/27

Table 43: Improvement for β = -2.30 Type-I Censoring C-optimal

When using a c-optimal design, the parameter estimates for α are expected to get worse compared with the balanced design. This only holds for the case where β is negative but not for when β is positive. The reason for that is that c-optimal design is estimating the β values much more accurate so the accuracy for α values gets worse. Table 43 and Table 44 shows that the highest improvement is when the proportion of censoring is 0.5. The percentages on the improvement tables are found by subtracting the MSE of the c-optimal design from the balanced design and dividing that subtraction by the MSE of the balanced design. This gives us the total improvement in the MSEs of the parameter estimates. The average increase in the accuracy for MSEs of the parameter estimates of β is 10% for exponential and Cox proportional hazards distribution. The MSEs of the parameter estimates for β values get better except for the Weibull distribution at the proportion level of 0.7. It can be seen that the patients are assigned mostly to support point 1 when β is negative and to support point 0 when β is positive.

α	-2.163			
β	-1.526			
Proportion of Censoring	0.1	0.3	0.5	0.7
Exponential α	0.022	0.027	0.038	0.066
Exponential β	0.046	0.067	0.108	0.210
Cox PH β	0.069	0.075	0.110	0.209
Weibull α	0.023	0.028	0.038	0.085
Weibull β	0.047	0.077	0.140	0.289

Table 41: MSE for β = -1.526 Type-I Censoring C-optimal

α	-2.163			
β	1.526			
Proportion of Censoring	0.1	0.3	0.5	0.7
Exponential α	0.025	0.038	0.067	0.140
Exponential β	0.046	0.064	0.103	0.203
Cox PH β	0.066	0.072	0.104	0.202
Weibull α	0.024	0.043	0.100	0.297
Weibull β	0.047	0.074	0.133	0.279

Table 42: MSE for β = 1.526 Type-I Censoring C-optimal

By looking at Table 41 and Table 42, it can be said that as β decreases the parameter estimates for both α and β gets better. When the proportion of censoring is low, the best estimates are for exponential and Weibull distribution. When the proportion of censoring increases, the parameter estimates for Weibull distribution are the worst. But the difference between the estimates of Weibull and exponential distribution is lower compared to the balanced design.

α	-2.163			
β	-1.526			
Proportion of Censoring	0.1	0.3	0.5	0.7
Exponential α	-7%	-22%	-35%	-49%
Exponential β	0%	3%	9%	17%
Cox PH β	0%	2%	9%	17%
Weibull α	-7%	-22%	-35%	-45%
Weibull β	0%	2%	4%	10%
Weight on 0/1	43/57	38/62	35/65	34/66

Table 46: Improvement for β = -1.526 Type-I Censoring C-optimal

α	-2.163			
β	1.526			
Proportion of Censoring	0.1	0.3	0.5	0.7
Exponential α	6%	17%	23%	29%
Exponential β	0%	5%	10%	16%
Cox PH β	1%	4%	9%	16%
Weibull α	6%	14%	13%	10%
Weibull β	0%	3%	5%	10%
Weight on 0/1	57/43	62/38	35/65	66/34

Table 45: Improvement for β = 1.526 Type-I Censoring C-optimal

When β is considered as -1.526, the MSEs of the parameter estimates for β with the exponential distribution and Cox proportional hazards model is approximately 10% better compared with the balanced design, whereas they are 5% better for the Weibull distribution. The MSEs of the parameter estimate of α values keep going worse as the proportion of censoring increases. Also for β values since the MSEs of the parameter estimates are worse for higher proportions, the increase in the accuracy is much higher compared with lower proportions. When β is considered as 1.526, MSEs of the parameter estimates for α and β get better as the proportion of censoring increases from 0.1 to 0.7. Again the MSEs of the parameter estimates for exponential and Cox proportional hazards distribution are approximately 10% better compared with the balanced design and 5% better for the Weibull distribution. As β value goes to 0, the highest increase in the accuracy of MSEs of the parameter estimates for β shifts from a proportion of censoring 0.5 to 0.7. The number of patients assigned to support point 1 increases with the increase in the proportion of censoring when β is negative. Also the number of patients assigned to support point 0 increases with the increase in the proportion of censoring when β is positive.

α	-2.163			
β	-0.69			
Proportion of Censoring	0.1	0.3	0.5	0.7
Exponential α	0.022	0.028	0.038	0.065
Exponential β	0.046	0.062	0.090	0.161
Cox PH β	0.050	0.063	0.089	0.159
Weibull α	0.023	0.028	0.040	0.094
Weibull β	0.046	0.064	0.096	0.180

Table 47: MSE for β = -0.69 Type-I Censoring C-optimal

α	-2.163			
β	0.69			
Proportion of Censoring	0.1	0.3	0.5	0.7
Exponential α	0.024	0.033	0.048	0.091
Exponential β	0.046	0.059	0.086	0.156
Cox PH β	0.050	0.060	0.086	0.154
Weibull α	0.024	0.035	0.063	0.169
Weibull β	0.047	0.062	0.093	0.173

Table 48: MSE for β = 0.69 Type-I Censoring C-optimal

As β goes to 0, the MSEs of the parameter estimates tend to become similar. They are still worse for Weibull distribution when the proportion of censoring increases.

α	-2.163			
β	-0.69			
Proportion of Censoring	0.1	0.3	0.5	0.7
Exponential α	-4%	-9%	-14%	-19%
Exponential β	0%	0%	1%	2%
Cox PH β	0%	0%	1%	2%
Weibull α	-4%	-9%	-14%	-16%
Weibull β	0%	1%	0%	1%
Weight on 0/1	46/54	44/56	43/57	42/58

Table 50: Improvement for β = -0.69 Type-I Censoring C-optimal

α	-2.163			
β	0.69			
Proportion of Censoring	0.1	0.3	0.5	0.7
Exponential α	4%	8%	12%	15%
Exponential β	0%	2%	3%	4%
Cox PH β	0%	2%	3%	4%
Weibull α	4%	8%	9%	7%
Weibull β	0%	2%	2%	3%
Weight on 0/1	54/46	56/44	57/43	58/42

Table 49: Improvement for β = 0.69 Type-I Censoring C-optimal

When β is considered as -0.69, the parameter estimates for β with the exponential distribution, Weibull distribution and Cox proportional hazards model is approximately 1% better compared with the balanced design. The estimate of α values keep going worse as the proportion of censoring increases. But the increase in the accuracy is still the lowest for Weibull distribution. Also for β values since the estimates are worse for higher proportions, the increase in the accuracy is much higher compared with lower proportions. When β is considered as 0.69, estimates for α and β get better as the proportion of censoring increases from 0.1 to 0.7. The MSEs of the parameter estimates for exponential distribution, Weibull distribution and Cox proportional hazards distribution are approximately 3% better compared with the balanced design. The increase in the accuracy of MSEs of the parameter estimates for $\beta = 0.69$ is much higher compared with $\beta = -0.69$. It can be seen that when β goes closer to 0, the weights tend to be closer to the balanced design whereas with bigger β values, the weights tend to depart from the balanced design.

4.2.2 Type-I Censoring for Weibull Data

α	-2.163			
β	-2.30			
γ	0.9			
Proportion of Censoring	0.1	0.3	0.5	0.7
Exponential α	-1%	-4%	-16%	-51%
Exponential β	0%	4%	19%	8%
Cox PH β	3%	5%	19%	9%
Weibull α	-2%	-7%	-19%	-47%
Weibull β	0%	2%	9%	-7%
Weight on 0/1	47/53	39/61	31/69	27/73

Table 52: Improvement for γ=0.9, β=-2.30 with Type-I Censoring

α	-2.163			
β	2.30			
γ	0.9			
Proportion of Censoring	0.1	0.3	0.5	0.7
Exponential α	2%	12%	31%	22%
Exponential β	0%	2%	17%	9%
Cox PH β	2%	4%	17%	10%
Weibull α	2%	9%	13%	-9%
Weibull β	0%	1%	6%	-7%
Weight on 0/1	53/47	61/39	69/31	73/27

Table 51: Improvement for γ=0.9, β=2.30 with Type-I Censoring

It can be seen that even the data is simulated with Weibull distribution, the c-optimal design for the exponential model are better compared with the balanced design. The MSEs for parameter estimates of exponential distribution and Cox PH model decrease approximately 10%. Again when a negative β value is used, MSEs of α values get worse. The c-optimal design assigns more patients to support point 0 when β is negative. By looking at Table 53 and Table 54, it can be seen that the increase in γ does not affect the optimal weights.

α	-2.163			
β	-2.30			
γ	1.1			
Proportion of Censoring	0.1	0.3	0.5	0.7
Exponential α	-2%	-9%	-23%	-58%
Exponential β	1%	8%	21%	9%
Cox PH β	3%	5%	19%	9%
Weibull α	-2%	-11%	-23%	-47%
Weibull β	1%	2%	3%	-12%
Weight on 0/1	47/53	39/61	31/69	27/73

Table 54: Improvement for γ=1.1, β=-2.30 with Type-I Censoring

α	-2.163			
β	2.30			
γ	1.1			
Proportion of Censoring	0.1	0.3	0.5	0.7
Exponential α	2%	14%	16%	27%
Exponential β	1%	7%	7%	5%
Cox PH β	2%	4%	8%	6%
Weibull α	2%	8%	-11%	-23%
Weibull β	1%	3%	-10%	-15%
Weight on 0/1	53/47	61/39	69/31	73/27

Table 53: Improvement for γ=1.1, β=2.30 with Type-I Censoring

As seen on Table 55 and Table 56, the change in shape parameter γ, still does not change the optimal weights. When shape parameter is higher and the distribution moves away from exponential, there is no increase in the accuracy of parameter estimates for Weibull regression. It can be concluded that, when the shape parameter increases the c-optimal designs are not efficient for data following Weibull distribution.

α	-2.163			
β	-2.30			
γ	2			
Proportion of Censoring	0.1	0.3	0.5	0.7
Exponential α	0%	0%	-1%	-3%
Exponential β	0%	1%	16%	10%
Cox PH β	3%	5%	18%	9%
Weibull α	0%	0%	-1%	0%
Weibull β	0%	0%	-1%	-3%
Weight on 0/1	47/53	39/61	31/69	27/73

Table 56: Improvement for γ=2, β=-2.30 with Type-I Censoring

α	-2.163			
β	2.30			
γ	2			
Proportion of Censoring	0.1	0.3	0.5	0.7
Exponential α	0%	1%	25%	19%
Exponential β	0%	2%	15%	11%
Cox PH β	2%	4%	17%	10%
Weibull α	0%	0%	-1%	-3%
Weibull β	0%	0%	-1%	-3%
Weight on 0/1	53/47	61/39	69/31	73/27

Table 55: Improvement for γ=2, β=2.30 with Type-I Censoring

4.2.3 Random Censoring

α	-2.163			
β	-2.30			
Proportion of Censoring	0.1	0.3	0.5	0.7
Exponential α	0.024	0.030	0.042	0.078
Exponential β	0.046	0.069	0.140	0.328
Cox PH β	0.102	0.105	0.145	0.323
Weibull α	0.025	0.032	0.043	0.093
Weibull β	0.047	0.084	0.218	0.577

Table 58: MSE for β = -2.30 Random Censoring C-optimal

α	-2.163			
β	2.30			
Proportion of Censoring	0.1	0.3	0.5	0.7
Exponential α	0.022	0.039	0.096	0.230
Exponential β	0.046	0.070	0.138	0.302
Cox PH β	0.101	0.105	0.148	0.307
Weibull α	0.022	0.047	0.166	0.505
Weibull β	0.047	0.086	0.213	0.488

Table 57: MSE for β = 2.30 Random Censoring C-optimal

When the optimal designs are used, as expected the parameter estimates for different distributions get better. By looking at Table 57 and Table 58, it can be said that as the proportion of censoring increases the parameter estimates get worse. The parameter estimates for α when a positive β value is used, are better compared with the negative β value with the same absolute value. As random censoring is used, the change in β from negative to positive has random effects on the accuracy of the estimates. The parameter estimates for β using an exponential distribution and Cox proportional hazards model tend to converge to a similar value whereas the Weibull distribution has the worst estimate when the proportion increases.

α	-2.163			
β	-2.30			
Proportion of Censoring	0.1	0.3	0.5	0.7
Exponential α	-19%	-49%	-75%	-99%
Exponential β	0%	5%	20%	9%
Cox PH β	4%	3%	18%	10%
Weibull α	-17%	-47%	-74%	-93%
Weibull β	0%	2%	7%	-13%
Weights on 0/1	42/58	34/66	29/71	26/74

Table 60: Improvement for β = -2.30 Random Censoring C-optimal

α	-2.163			
β	2.30			
Proportion of Censoring	0.1	0.3	0.5	0.7
Exponential α	12%	23%	34%	25%
Exponential β	0%	4%	19%	13%
Cox PH β	4%	3%	16%	11%
Weibull α	12%	18%	17%	-4%
Weibull β	-1%	0%	7%	-4%
Weights on 0/1	58/42	66/34	71/29	74/26

Table 59: Improvement for β = 2.30 Random Censoring C-optimal

When using a c-optimal design, as it is expected that the MSEs of the parameter estimates for α get worse compared with the balanced design. This only holds for the case where β is negative but not for when β is positive. The reason for that is that c-optimal design is estimating the β values much more accurate so the accuracy for α values gets worse. The highest improvement is when the proportion of censoring is 0.5. The average increase in the accuracy of MSEs of the parameter estimate of β is 9% for exponential and Cox proportional hazards distribution. The MSEs of the parameter estimates for β values get better except for the Weibull distribution at the proportion level of 0.7. This is caused by the same error in the R software.

α	**-2.163**			
β	**-1.526**			
Proportion of Censoring	**0.1**	**0.3**	**0.5**	**0.7**
Exponential α	0.023	0.028	0.039	0.067
Exponential β	0.045	0.064	0.103	0.206
Cox PH β	0.065	0.072	0.105	0.204
Weibull α	0.024	0.029	0.040	0.085
Weibull β	0.046	0.073	0.134	0.292

Table 61: MSE for β = -1.526 Random Censoring C-optimal

α	**-2.163**			
β	**1.526**			
Proportion of Censoring	**0.1**	**0.3**	**0.5**	**0.7**
Exponential α	0.023	0.037	0.065	0.140
Exponential β	0.046	0.066	0.104	0.207
Cox PH β	0.066	0.074	0.106	0.206
Weibull α	0.022	0.043	0.099	0.302
Weibull β	0.047	0.076	0.135	0.289

Table 62: MSE for β = 1.526 Random Censoring C-optimal

By looking at Table 61 and Table 62, it can be said that as β decreases the MSEs of the parameter estimates for both α and β gets better. When the proportion of censoring is low, the best estimates are for exponential and Weibull distribution. When the proportion of censoring increases, the MSEs of the parameter estimates for Weibull distribution are the worst. But the difference between the MSEs of the parameter estimates of Weibull and exponential distribution is lower compared to the balanced design.

α	-2.163			
β	-1.526			
Proportion of Censoring	0.1	0.3	0.5	0.7
Exponential α	-16%	-32%	-43%	-50%
Exponential β	1%	5%	10%	15%
Cox PH β	2%	2%	9%	15%
Weibull α	-15%	-31%	-43%	-46%
Weibull β	1%	3%	5%	6%
Weights on 0/1	43/57	38/62	35/65	34/66

Table 63: Improvement for β = -1.526 Random Censoring C-optimal

α	-2.163			
β	1.526			
Proportion of Censoring	0.1	0.3	0.5	0.7
Exponential α	11%	18%	24%	29%
Exponential β	0%	2%	9%	15%
Cox PH β	0.3%	0.1%	8%	14%
Weibull α	11%	15%	15%	9%
Weibull β	-1%	1%	5%	7%
Weights on 0/1	57/43	62/38	65/35	6/34

Table 64: Improvement for β = 1.526 Random Censoring C-optimal

When β is considered as -1.526, the MSEs of the parameter estimates for β with the exponential distribution and Cox proportional hazards model is approximately 10% better compared with the balanced design, whereas they are 5% better for the Weibull distribution. The MSEs of the parameter estimate of α values keep going worse as the proportion of censoring increases. Also for β values since the estimates are worse for higher proportions, the increase in the accuracy is much higher compared with lower proportions. When β is considered as 1.526, MSEs of the parameter estimates for α and β get better as the proportion of censoring increases from 0.1 to 0.7. Again the MSEs of the parameter estimates for exponential and Cox proportional hazards distribution are approximately 10% better compared with the balanced design and 5% better for the Weibull distribution. As β value goes to 0, the highest increase in the accuracy of MSEs of the parameter estimates for β shifts from the proportion of censoring 0.5 to 0.7.

α	-2.163			
β	-0.69			
Proportion of Censoring	0.1	0.3	0.5	0.7
Exponential α	0.022	0.028	0.039	0.066
Exponential β	0.045	0.060	0.086	0.157
Cox PH β	0.049	0.061	0.086	0.156
Weibull α	0.023	0.028	0.041	0.094
Weibull β	0.045	0.062	0.092	0.176

Table 66: MSE for β = -0.69 Random Censoring C-optimal

α	-2.163			
β	0.69			
Proportion of Censoring	0.1	0.3	0.5	0.7
Exponential α	0.023	0.032	0.048	0.090
Exponential β	0.046	0.060	0.087	0.152
Cox PH β	0.049	0.061	0.087	0.151
Weibull α	0.023	0.034	0.063	0.169
Weibull β	0.046	0.062	0.094	0.171

Table 65: MSE for β = 0.69 Random Censoring C-optimal

As β goes to 0, the MSEs of the parameter estimates tend to become similar. They are still worse for Weibull distribution when the proportion of censoring increases.

α	-2.163			
β	-0.69			
Proportion of Censoring	0.1	0.3	0.5	0.7
Exponential α	-8%	-13%	-17%	-20%
Exponential β	0%	1%	3%	3%
Cox PH β	0%	0.4%	3%	3%
Weibull α	-8%	-13%	-16%	-15%
Weibull β	1%	1%	2%	1%
Weights on 0/1	46/54	44/56	43/57	42/58

Table 68:Improvement for β = -0.69 Random Censoring C-optimal

α	-2.163			
β	0.69			
Proportion of Censoring	0.1	0.3	0.5	0.7
Exponential α	6%	10%	12%	13%
Exponential β	-1%	0.5%	2%	4%
Cox PH β	-1%	0.5%	2%	4%
Weibull α	6%	9%	9%	6%
Weibull β	-1%	0.2%	1%	2%
Weights on 0/1	54/46	56/44	57/43	58/42

Table 67: Improvement for β = 0.69 Random Censoring C-optimal

When β is considered as -0.69, the MSEs of the parameter estimates for β with the exponential distribution, Weibull distribution and Cox proportional hazards model are approximately 1% better compared with the balanced design. The MSEs of the parameter estimate of α values keep getting worse as the proportion of censoring increases. But the increase in the accuracy is still the lowest for Weibull distribution. Also for β values since the MSEs of the parameter estimates are worse for higher proportions, the increase in the accuracy is much higher compared with lower proportions. When β is considered as 0.69, the MSEs of the parameter estimates for α and β get better as the proportion of censoring increases from 0.1 to 0.7. The MSEs of the parameter estimates for exponential distribution, Weibull distribution and Cox proportional hazards distribution are approximately 3% better compared with the balanced design. The increase in the accuracy of MSEs of the parameter estimates for $\beta = 0.69$ is much higher compared with $\beta = -0.69$.

4.2.4 Locally C-optimal Design

The c-optimal designs that were considered so far are locally optimal in that they depend on the values for α and β. But those values would be unknown in practice. Now, it will be investigated how robust these designs are if the parameter values are misspecified. In this study negative β values are taken. If we consider the corresponding positive β values nearly all of the c-efficiencies are 100%. The reason behind this is that the corresponding weights are nearly 0.5 which yields with 100% in c-efficiencies. Two different types of censoring is used: type-I and random. 5 different parameter vectors are formed with the same α value and different β values of the form $\gamma_i = (\alpha_i, \beta_i)$. The α value was chosen to have a realistic value. It was the estimated α value in the leukaemia study by (Freireich, et al., 1963). The reason why α value is kept constant is that the change in the baseline hazard does not affect the efficiency whereas the change in β values changes the efficiencies as well. The assumed values and the true values are compared in order to find the highest minimum c-efficiency of a parameter vector. The locally c-optimal designs have support points 0 and 1. The corresponding weights were found using (3.4) and are shown in Table 69 with the c-efficiencies of each the designs when the parameter values are misspecified.

		Design				
Parameter Vector	**Weight on 1**	ξ_{γ_0}	ξ_{γ_1}	ξ_{γ_2}	ξ_{γ_3}	ξ_{γ_4}
$\boldsymbol{\gamma_0} = (\mathbf{-2.163, -0.10})$	0.50	1	0.9986	0.9783	0.9172	0.7348
$\boldsymbol{\gamma_1} = (\mathbf{-2.163, -0.69})$	0.52	0.9986	1	0.9879	0.9361	0.7633
$\boldsymbol{\gamma_2} = (\mathbf{-2.163, -1.526})$	0.58	0.9787	0.9881	1	0.9790	0.8449
$\boldsymbol{\gamma_3} = (\mathbf{-2.163, -2.30})$	0.65	0.9236	0.9410	0.9803	1	0.9345
$\boldsymbol{\gamma_4} = (\mathbf{-2.163, -3.51})$	0.76	0.7910	0.8146	0.8791	0.9469	1

Table 69: Locally c-optimal Type-I censoring

The locally c-optimal designs with type-I censoring have high c-efficiencies except for when β value is -3.51. Having a high β value decreases the c-efficiencies of all the locally c-optimal designs. The lowest efficiency 0.7348 is when the assumed value is $\boldsymbol{\gamma_4}$ and the true value is $\boldsymbol{\gamma_0}$. The design with β value -2.30 has the highest minimum efficiency with 0.9236 is near to the centre of parameter space but more closer to the highest β value which makes it more robust than the other designs. By looking at the weights as it was concluded before the weight on support point 1 increases as β values moves away from 0.

		Design				
Parameter Vector	**Weight on 1**	$\xi_{\gamma 0}$	$\xi_{\gamma 1}$	$\xi_{\gamma 2}$	$\xi_{\gamma 3}$	$\xi_{\gamma 4}$
$\boldsymbol{\gamma_0} = (-\mathbf{2.163}, -\mathbf{0.10})$	0.51	1	0.9951	0.9562	0.8714	0.6668
$\boldsymbol{\gamma_1} = (-\mathbf{2.163}, -\mathbf{0.69})$	0.54	0.9952	1	0.9801	0.9127	0.7217
$\boldsymbol{\gamma_2} = (-\mathbf{2.163}, -\mathbf{1.526})$	0.61	0.9582	0.9807	1	0.9752	0.8318
$\boldsymbol{\gamma_3} = (-\mathbf{2.163}, -\mathbf{2.30})$	0.68	0.8867	0.9231	0.9774	1	0.9335
$\boldsymbol{\gamma_4} = (-\mathbf{2.163}, -\mathbf{3.51})$	0.79	0.7520	0.7961	0.8772	0.9485	1

Table 70: Locally c-optimal random censoring

The locally c-optimal designs with random censoring have high c-efficiencies except for when β value is -3.51. All of the efficiencies are lower compared with type-I censoring. Having a high β value decreases the c-efficiencies of all the locally c-optimal designs. The lowest efficiency 0.668 is when the assumed value is $\boldsymbol{\gamma_4}$ and the true value is $\boldsymbol{\gamma_0}$. The design with β value -2.30 has the highest minimum efficiency with 0.8867 is near to the centre of parameter space but more closer to the highest β value which makes it more robust than the other designs. By looking at the weights as it was concluded before the weight on support point 1 increases as β values moves away from 0.

This shows that it is important to consider carefully which parameters to choose for finding the c-optimal design. It is advisable to construct a table like Table 69 or Table 70 in order to find a design that has high efficiency across the board. Alternatively, standardised maximin designs could be considered.

4.2.5 Standardised Maximin Design

Standardised maximin c-optimal design for β, is a design ξ* maximising the criterion

$$\phi(\xi) = min\left\{\frac{(0\ 1)\ M^{-}(,\alpha,\beta)\begin{pmatrix}0\\1\end{pmatrix}}{(0\ 1)\ M^{-}(\xi,\alpha,\beta)\begin{pmatrix}0\\1\end{pmatrix}}\ \beta\ \epsilon[\beta_0,\beta_1]\right\},$$

where ξ_β^* is the locally optimal design. It searches in a range of β's the design having the highest minimum efficiency and assigns that as the standardised maximin design (Dette, 1997).

For type-I censoring, the standardised maximin c-optimal design allocates 37% of the observations to the support point $x = 0$ and 63% of them to the support point $x = 1$. It is locally c-optimal for $\boldsymbol{\gamma_5} = (-2.163, -2.25)$ and the minimum efficiency is 0.9282 at parameter vector $\boldsymbol{\gamma_0}$. The parameter vector $\boldsymbol{\gamma_5}$ has efficiencies 0.9452, 0.9824, 0.9828 and 0.9292 respectively for parameter vectors $\boldsymbol{\gamma_1}$, $\boldsymbol{\gamma_2}$, $\boldsymbol{\gamma_3}$, $\boldsymbol{\gamma_4}$.

For random censoring, the standardised maximin c-optimal design allocates 34% of the observation to the support point $x = 0$ and 66% of them to the support point $x = 1$. It is locally c-optimal for $\boldsymbol{\gamma_5} = (-2.163, -2.09)$ and the minimum efficiency is 0.9087 at parameter vector $\boldsymbol{\gamma_4}$. The parameter vector $\boldsymbol{\gamma_5}$ has efficiencies 0.9088, 0.9421, 0.9879 and 0.9981 respectively for parameter vectors $\boldsymbol{\gamma_0}$, $\boldsymbol{\gamma_1}$, $\boldsymbol{\gamma_2}$, $\boldsymbol{\gamma_3}$. It can be seen that the standardised maximin design has high efficiency for a large range of parametric values.

In real life β value is unknown, so it is important to look for scenarios on how MSEs for parameter estimates changes when the parameter values are misspecified. In order to search that specific problem, the standardised maximin c-optimal design was found with $\beta_{min} = -0.69$ and $\beta_{max} = -2.30$. It was seen that the standardised maximin design is locally c-optimal for $\beta = -1.63$. The new MSEs for parameter estimates are calculated using $\beta = -0.69, -1.526$ and -2.30. A new dataset was simulated for the balanced design using censoring times of the standardised maximin design. A second dataset was simulated for the c-optimal design using the corresponding weights and censoring times of the standardised maximin design. Table 71 shows the percentage change for balanced design and standardised maximin design.

$\alpha = -2.163$ $\beta = -1.63$												
β **of the Design**												
Proportion of Censoring	**0.1**	**0.3**	**0.5**	**0.7**	**0.1**	**0.3**	**0.5**	**0.7**	**0.1**	**0.3**	**0.5**	**0.7**
Exponential α	-7%	-22%	-38%	-54%	-7%	-22%	-38%	-54%	-7%	-22%	-38%	-54%
Exponential β	0%	8%	20%	4%	0%	3%	9%	17%	-1%	-1%	-1%	-1%
Cox PH β	2%	6%	19%	4%	0%	2%	9%	17%	0%	-1.5%	-1%	0%
Weibull α	-7%	-22%	-38%	-53%	-7%	-22%	-38%	-50%	-7%	-21%	-38%	-47%
Weibull β	0%	3%	9%	-10%	0%	1%	3%	10%	-1%	-1%	-2%	-2%
Weights on 0	47	41	36	39	47	41	36	39	47	41	36	39

Table 71: Standardised Maximin Design Comparison of Balanced and C-optimal Deisgn for β= -2.30,-1.526 and -0.69 respectively

By looking at the MSEs for parameter estimates it can be seen that, even though the parameters are not known, the standardised maximin design has better parameter estimates compared with the balanced design. The MSEs for parameter estimates are approximately 8% lower for exponential and Cox PH model. The highest increase in the accuracy is at proportion of censoring 0.5 for $\beta = -2.30$ whereas it is highest at 0.7 when $\beta = -1.526$. There is still a software error causing MSE of the Weibull model at proportion of censoring 0.7 to go worse. When β value is closer to 0, the parameter estimates are either similar or a little worse. But in general using the standardised maximin design instead of the balanced design gives better parameter estimates compared to the balanced design so it is recommend to use those designs instead of balanced designs.

4.2.6 C-optimal Design with Optimal Support Points

The case where support points are binary is solved in the previous parts. In this part the case of optimal support points where x can take values on a continuous scale in $[0, \infty)$ will be examined for different β values. Type-I censoring is assumed for the purpose of this part. When β is negative, the lower support point is 0 and the other optimal support point x_2 is the unique solution of the equation (3.6). The optimal support points (x_1, x_2) are given in Table 72.

	Proportion of Censoring				
$\boldsymbol{\beta}$	0.1	0.3	0.5	0.7	0.9
-3.51	(0,0.95)	(0,0.70)	(0,0.39)	(0,0.31)	(0,0.28)
-2.30	(0,1.19)	(0,0.90)	(0,0.72)	(0,0.64)	(0,0.59)
-1.526	(0,1.79)	(0,1.50)	(0,1.37)	(0,1.28)	(0,1.23)
-0.69	(0,5.56)	(0,5.29)	(0,5.15)	(0,5.06)	(0,4.99)

Table 72: Optimal Support Points

It can be seen that as β values comes closer to 0, the interval between the optimal support points increases and it decreases as the proportion of censoring increases. They are mostly similar to a binary case but for $\beta = -0.69$, the support points change a lot. By looking at Table 73 and Table 74, it can be said

$\boldsymbol{\alpha}$	**-2.163**			
$\boldsymbol{\beta}$	**-2.30**			
Proportion of Censoring	**0.1**	**0.3**	**0.5**	**0.7**
Exponential $\boldsymbol{\alpha}$	-25%	-23%	-23%	-12%
Exponential $\boldsymbol{\beta}$	20%	15%	11%	8%
Cox PH $\boldsymbol{\beta}$	18%	14%	11%	9%
Weibull $\boldsymbol{\alpha}$	-23%	-19%	-14%	-11%
Weibull $\boldsymbol{\beta}$	22%	9%	6%	4%
Weights on 0	45	31	33	34

Table 74:Improvement for β = -2.30 Type-I Censoring Optimal Support Points

$\boldsymbol{\alpha}$	**-2.163**			
$\boldsymbol{\beta}$	**-1.526**			
Proportion of Censoring	**0.1**	**0.3**	**0.5**	**0.7**
Exponential $\boldsymbol{\alpha}$	-23%	-21%	-21%	-14%
Exponential $\boldsymbol{\beta}$	51%	32%	24%	16%
Cox PH $\boldsymbol{\beta}$	34%	32%	24%	17%
Weibull $\boldsymbol{\alpha}$	-25%	-21%	-21%	-18%
Weibull $\boldsymbol{\beta}$	40%	17%	12%	3%
Weights on 0	38	34	31	30

Table 73:Improvement for β = -1.526 Random Censoring Optimal Support Points

that the MSEs of the parameter estimates with optimal support points and a c-optimal design are the best results. Those results are compared with the c-optimal design using binary support points.

4.3 C-efficiency

Table 75 and Table 76 show the c-efficiencies compared with the balanced design and corresponding weight on support point $x = 1$ with Type-I censoring. It can be seen that c-efficiencies increase as β moves closer to 0 and decreases as the proportion of censoring increases. Also the c-efficiencies are symmetrical for same β values with opposite signs. When the proportion of censoring is 0.1 almost all the c-efficiencies are 100%. The efficiencies for bigger β values decrease drastically when the proportion of censoring is more than 0.5. The reason behind this is that the optimal design tends to assign more patients where it is more difficult to estimate in order to increase its accuracy. In this case the optimal design tends to put more weight on support point $x = 1$ when β values are negative and on support point $x = 0$ when β values are positive.

Proportion of Censoring	β									
	-3.51	**-2.3**	**-1.526**	**-0.69**	**-0.1**	**0.1**	**0.69**	**1.526**	**2.3**	**3.51**
0.1	99 (0.53)	99 (0.53)	99 (0.53)	99 (0.52)	100 (0.50)	100 (0.50)	99 (0.48)	99 (0.47)	99 (0.47)	99 (0.47)
0.3	95 (0.61)	95 (0.61)	97 (0.59)	99 (0.54)	99 (0.51)	99 (0.49)	99 (0.46)	97 (0.41)	95 (0.39)	95 (0.39)
0.5	69 (0.78)	85 (0.69)	93 (0.63)	98 (0.56)	99 (0.51)	99 (0.49)	98 (0.44)	93 (0.37)	85 (0.31)	69 (0.22)
0.7	57 (0.83)	79 (0.73)	90 (0.66)	97 (0.57)	99 (0.51)	99 (0.49)	97 (0.43)	90 (0.34)	79 (0.27)	57 (0.17)
0.9	52 (0.85)	75 (0.75)	88 (0.67)	97 (0.58)	99 (0.51)	99 (0.49)	97 (0.42)	88 (0.33)	75 (0.25)	52 (0.15)

Table 75: C-efficiencies Type-I Censoring Positive α

The change in α does not affect the c-efficiencies. The weights in the support points does not change with α and so as the c-efficiencies.

Proportion of Censoring	β									
	-3.51	**-2.3**	**-1.526**	**-0.69**	**-0.1**	**0.1**	**0.69**	**1.526**	**2.3**	**3.51**
0.1	99 (0.53)	99 (0.53)	99 (0.53)	99 (0.52)	100 (0.50)	100 (0.50)	99 (0.48)	99 (0.47)	99 (0.47)	99 (0.47)
0.3	95 (0.61)	95 (0.61)	97 (0.59)	99 (0.54)	99 (0.51)	99 (0.49)	99 (0.46)	97 (0.41)	95 (0.39)	95 (0.39)
0.5	69 (0.78)	85 (0.69)	93 (0.63)	98 (0.56)	99 (0.51)	99 (0.49)	98 (0.44)	93 (0.37)	85 (0.31)	69 (0.22)
0.7	57 (0.83)	79 (0.73)	90 (0.66)	97 (0.57)	99 (0.51)	99 (0.49)	97 (0.43)	90 (0.34)	79 (0.27)	57 (0.17)
0.9	52 (0.85)	75 (0.75)	88 (0.67)	97 (0.58)	99 (0.51)	99 (0.49)	97 (0.42)	88 (0.33)	75 (0.25)	52 (0.15)

Table 76: C-efficiencies Type-I Censoring Negative α

Table 77 and Table 78 show the c-efficiencies compared with the balanced design and corresponding weight on support point $x = 1$ with random censoring. It can be seen that c-efficiencies increase as β moves closer to 0 and decreases as the proportion of censoring increases. Also the c-efficiencies are symmetrical for same β values with opposite signs. When the proportion of censoring is 0.1 all the c-efficiencies are 100%. The efficiencies for bigger β values decrease drastically when the proportion of censoring is more than 0.5. C-optimal design tends to put more weight on support point $x = 1$ when β values are positive and on support point $x = 0$ when β values are negative.

Proportion of Censoring	**β**									
	-3.51	**-2.3**	**-1.526**	**-0.69**	**-0.1**	**0.1**	**0.69**	**1.526**	**2.3**	**3.51**
0.1	97 (0.42)	98 (0.42)	98 (0.43)	99 (0.46)	100 (0.49)	100 (0.51)	99 (0.54)	98 (0.57)	98 (0.58)	97 (0.58)
0.3	88 (0.32)	90 (0.34)	94 (0.38)	99 (0.44)	100 (0.49)	100 (0.51)	99 (0.56)	94 (0.62)	90 (0.66)	88 (0.68)
0.5	63 (0.20)	82 (0.29)	91 (0.35)	98 (0.43)	100 (0.49)	100 (0.51)	98 (0.57)	91 (0.65)	82 (0.71)	63 (0.80)
0.7	55 (0.17)	77 (0.26)	89 (0.34)	98 (0.42)	100 (0.49)	100 (0.51)	98 (0.58)	89 (0.66)	77 (0.74)	55 (0.83)
0.9	52 (0.85)	74 (0.75)	88 (0.32)	97 (0.42)	100 (0.49)	100 (0.51)	97 (0.58)	88 (0.68)	74 (0.75)	52 (0.85)

Table 77: C-efficiencies Random Censoring Positive α

The change in α does not also change the c-efficiencies for random censoring. So α has no effect on the weights for random censoring.

Proportion of Censoring	**β**									
	-3.51	**-2.3**	**-1.526**	**-0.69**	**-0.1**	**0.1**	**0.69**	**1.526**	**2.3**	**3.51**
0.1	97 (0.42)	98 (0.42)	98 (0.43)	99 (0.46)	100 (0.49)	100 (0.51)	99 (0.54)	98 (0.57)	98 (0.58)	97 (0.58)
0.3	88 (0.32)	90 (0.34)	94 (0.38)	99 (0.44)	100 (0.49)	100 (0.51)	99 (0.56)	94 (0.62)	90 (0.66)	88 (0.68)
0.5	63 (0.20)	82 (0.29)	91 (0.35)	98 (0.43)	100 (0.49)	100 (0.51)	98 (0.57)	91 (0.65)	82 (0.71)	63 (0.80)
0.7	55 (0.17)	77 (0.26)	89 (0.34)	98 (0.42)	100 (0.49)	100 (0.51)	98 (0.58)	89 (0.66)	77 (0.74)	55 (0.83)
0.9	52 (0.85)	74 (0.75)	88 (0.32)	97 (0.42)	100 (0.49)	100 (0.51)	97 (0.58)	88 (0.68)	74 (0.75)	52 (0.85)

Table 78: C-efficiencies Random Censoring Negative α

5. Discussion and Recommendations

Time-to-event data usually has heavy censoring and it is important to find an optimal design to overcome with the negative effects of censoring. To overcome this effect c-optimal designs are used and they are found to be more accurate than balanced designs to estimate the model parameters. It was found that even though the time-to-event data follow an exponential distribution, a Cox proportional hazards model can estimate the coefficient of the hazard covariate more accurately when a c-optimal design is used. It was seen that the increase in the proportion of censoring decreases the accuracy of the estimates so a c-optimal design is necessary for heavily censored data. Because the usage of a c-optimal design helps us get better estimates which eventually affects all the design process. It was expected to see the accuracy increase with c-optimal designs compared with the balanced design. The only inconsistency was in the Weibull distribution, the estimates of this distribution were quite unexpected. This was caused by the software that was used during the analysis. The statistical package R could not converge correctly when there was heavy censoring. In practice, when the data follows an exponential distribution it is highly efficient to use the c-optimal designs. When the data follows a Weibull distribution, if the shape parameter is not too high is it still efficient to use c-optimal designs for the exponential model. When the shape parameter increases and the distribution becomes less exponential, the c-optimal design is not efficient enough.

In the study, mostly the data used was assumed to be with an exponential distribution but some calculations with a Weibull distribution was also made. The usage of a Weibull distribution can be extended for future research. By simulating the data for a Weibull distribution, it could be checked if the c-optimal designs for the exponential model are still better than the balanced design even though the data are not exponential. This was proven but only with a small shape parameter. Also, it could be investigated if the c-optimal design gives a smaller bias or MSE than the balanced design if these data are wrongly analysed as an exponential model. It could also be used to compare the c-optimal designs for the exponential model with those for the Weibull model, which are much harder to find, in order to see if the c-optimal designs for the exponential model can be recommended in this situation. In this study, it was seen by just doing a small analysis that in some cases, they can be recommended.

6. References

Collett, D. (2014). *Modelling Survival Data in Medical Research, Third Edition.* Chapman and Hall/CRC.

Cox, D. (1972). Regression Models and Life-Tables. *Journal of the Royal Statistics Society*, 187-220.

Dette, H. (1997). Designing experiments with Respect to "Standardised" Optimality Criteria. *Royal Statistical Society*, 59, No. 1, 97-110.

Freireich, E., Gehan, E., Frei, E., Schroeder, L., Wolman, I., Anbari, R., . . . Lee, S. (1963). The Effect of 6-Mercaptopurine on the Duration of Steroid-induced Remissions in Acute Leukemia: A Model for Evaluation of Other Potentially Useful Therapy. *Blood*, 699-716.

Kimber, A. (2015). Survival Analysis Lectures.

Konstantinou, M., Biedermann, S., & Kimber, A. (2014). *Optimal Designs For Two-parameter Nonlinear Models With Application To Survival Models.* University of Southampton: Southampton Statistical Research Institue.

Konstantinou, M., Biedermann, S., & Kimber, A. (2015). Optimal Designs For Full and Partial Likelihood Information - With Application To Survival Models. *Journal of Statistical Planning and Inference*, Volume 165, 27-37.

Rivas-Lopez, M., Lopez-Fidalgo, J., & Campo, R. D. (2014). Optimal experimental designs for accelerated failure time with Type I and random censoring. *Biometrical*, 819-837.

Schmidt, D., & Schwabe, R. (2015). Optimal Designs for Censored Data. *Metrika*, Volume 78, 237-257.

7. Appendices

The R code used in the study:

7.1 R Code for Finding Optimal Design

```
#Type-I censoring for exponential data

#Proportion of censoring

Proportion <- function(x,cen,alpha,beta) {

x1<-rep(0:0.9, each=x)

myrate <- exp(beta*x1+alpha)

y <- rexp(length(x1),rate=myrate)

ycen <- pmin(y, cen)

di <- as.numeric(y <= cen) # 0 as censored

return(length(which(di==0))/length(di))}

#running the proportion code

set.seed(1234)

x<- 50

cen<- 10.425

alpha<- -2.163

beta<- -2.3

result <- matrix(NA, nrow=1, ncol=1000)

for(i in 1:1000) result[,i]<-Proportion(x,cen,alpha,beta)

mean(result)

##C-optimal design for exponential distribution

x1<- 0

x2<- 1

cen <- 15.7

qfunc1<-(1-exp(-cen*exp(alpha+beta*x1)))

qfunc2<-(1-exp(-cen*exp(alpha+beta*x2)))

w1n<- sqrt(qfunc2)

w1d<- sqrt(qfunc1) + sqrt(qfunc2)

w1<- w1n/w1d

w2n<- sqrt(qfunc1)

w2d<- sqrt(qfunc1) + sqrt(qfunc2)
```

```
w2<- w2n/w2d
##C-optimal design for Weibull distribution
x1<- 0
x2<- 1
gamma<- 2
cen <- 2.12
qfunc1<-(1-exp(-cen^gamma*exp(alpha+beta*x1)))
qfunc2<-(1-exp(-cen^gamma*exp(alpha+beta*x2)))
w1n<- sqrt(qfunc2)
w1d<- sqrt(qfunc1) + sqrt(qfunc2)
w1<- w1n/w1d
w2n<- sqrt(qfunc1)
w2d<- sqrt(qfunc1) + sqrt(qfunc2)
w2<- w2n/w2d
#c-Efficiency with balanced design
w1<-0.5
w2<-0.5
effiup<- w11*w21
effidown<- w21*(w1)^2 + w11* (w2)^2
cefficiency <- effiup/effidown
##function for efficiency
efficiency<-function(beta0,beta2,beta3,beta4) {
cen <- 30 # Censoring time
alpha1 <- -2.163 # Alpha
beta <- c(beta2,beta3,beta4) # Matrix of betas
cefficiency <- matrix(NA,ncol=3) # empty efficiency matrix
qfunc <-(1-exp(-cen*exp(alpha1+beta0*x1)))
qfunc20 <-(1-exp(-cen*exp(alpha1+beta0*x2)))
w1 <- sqrt(qfunc20)/(sqrt(qfunc) + sqrt(qfunc20))
w2 <- sqrt(qfunc)/(sqrt(qfunc) + sqrt(qfunc20))
for (i in 1:3){
qfunc1 <- (1-exp(-cen*exp(alpha1+beta[i]*x1)))
```

```
qfunc2 <- (1-exp(-cen*exp(alpha1+beta[i]*x2)))
w11 <- sqrt(qfunc2)/(sqrt(qfunc1) + sqrt(qfunc2))
w21 <- sqrt(qfunc1)/(sqrt(qfunc1) + sqrt(qfunc2))
cefficiency[i] <- (w11*w21) / (w21*(w1)^2 + w11* (w2)^2)}
#return(cefficiency[])
return(min(cefficiency[])) }
## Standardised Maximin Design
betamin<- -0.69
betamaxi<- -2.30
cen<-30
qfuncmin1<-(1-exp(-cen*exp(alpha+betamin*x1)))
qfuncmin2<-(1-exp(-cen*exp(alpha+betamin*x2)))
wmin1n<- sqrt(qfuncmin2)
wmin2d<- sqrt(qfuncmin1) + sqrt(qfuncmin2)
wmin1<- wmin1n/wmin2d
qfuncmaxi1<-(1-exp(-cen*exp(alpha+betamaxi*x1)))
qfuncmaxi2<-(1-exp(-cen*exp(alpha+betamaxi*x2)))
wmaxi2n<- sqrt(qfuncmaxi2)
wmaxi2d<- sqrt(qfuncmaxi1) + sqrt(qfuncmaxi2)
wmaxi2<- wmaxi2n/wmaxi2d
wb0<- wmin1
wb1<- wmaxi2
w1maximin<- (wb0+wb1)/2
w2maximin<- 1 - w1maximin
#Random censoring - proportion
Proportion2 <- function(x,censor,alpha,beta) {
x1<-rep(0:1, each=x)
myrate <- exp(beta*x1+alpha)
y <- rexp(length(x1),rate=myrate)
zcen<- runif(length(x1))
cen<-censor-zcen
ycen <- pmin(y, cen)
```

```
di <- as.numeric(y <= cen) # 0 as censored

return(length(which(di==0))/length(di))}

#Random Censoring Q function

qfunc1<- 1 + (exp(- cen * exp(alpha+beta*x1))-1) / (cen *exp(alpha+beta*x1))

qfunc2<- 1 + (exp(- cen * exp(alpha+beta*x2))-1) / (cen *exp(alpha+beta*x2))
```

7.1 R Code for Finding MSEs

```
##Type 1 censored data simulation

Simulation2 <- function(x , inputrates,cen) {

y <- rexp(length(inputrates), rate=inputrates)

obs <- pmin(y, cen)

di <- as.numeric(y <= cen)

temp1 <- survreg(Surv(obs, di)~x, dist="exponential")

temp2 <- coxph(Surv(obs, di)~x)

temp3 <- survreg(Surv(obs, di)~x, dist="weibull")

return(c(temp1$coef[1], temp1$coef[2],temp2$coef,temp3$coef[1],temp3$coef[2])) }

#running the simulation

set.seed(1234)

cen <- 139.35

result2 <- matrix(NA, nrow=5, ncol=10000)

for(i in 1:10000) result2[,i]<-Simulation2(x,myrate,cen)

Simulation2(x,myrate,cen)

#finding MSEs

resultnew<-result2[,colSums(result2 <= -7 | result2 >= 7) == 0]

MSE_1 <- sum((resultnew[1,] + alpha) ^ 2) / length(resultnew[1,])

MSE_2 <- sum((resultnew[2,] + beta) ^ 2) / length(resultnew[2,])

MSE_3 <- sum((resultnew[3,] - beta) ^ 2) / length(resultnew[3,])

MSE_4 <- sum((resultnew[4,] + alpha) ^ 2) / length(resultnew[4,])

MSE_5 <- sum((resultnew[5,] + beta) ^ 2) / length(resultnew[5,])
```