Assignment #2 Appendix

1. Exploratory Data Analysis

Experiment:

- Treatment #1: Argon laser treatment in either the left or right eye
- Treatment #2: Xenon laser treatment in either the left or right eye
- Control: No laser treatment in the eye that did NOT receive the treatment.
- Outcome: A drop in visual acuity in each eye below 5/200 for two visits in a row

Research Question:

1. Determine the efficacy of treatment type on visual acuity and quantify the improvement between eyes by treatment type do a good job at slowing down deterioration in eye sight. There was no difference in the performance of the two treatment groups - both did equally a good job.
2. Understand the potential impact that age at diagnosis and clinical risk of diabetic retinopathy have on visual acuity.

Variables

Variable Name	Description
`id`	Subject ID
`laser`	Type of treatment that was used, either xenon or argon
`eye`	left or right eye which received treatment for each participant
`age`	age in years at time of diabetes diagnosis
`type`	adult or juvenile at time of diabetes diagnosis
`trt`	0 for control eye, 1 for treated eye
`futime`	lag-corrected time to loss of vision or last follow-up in months
`status`	0 for lost to follow-up, 1 for loss of vision in eye
`risk`	clinical risk of lost of acuity. Must be at least 6 in one eye to participate in study.

Data Cleaning

Summary of data (at the eye level)

```
##        id           laser        eye           age              type
##  Min.   :   5.0   argon:194   left :216   Min.   : 1.00   adult   :166
##  1st Qu.: 480.0   xenon:200   right:178   1st Qu.:10.00   juvenile:228
```

```
##  Median : 834.0                          Median :16.00
##  Mean   : 873.2                          Mean   :20.78
##  3rd Qu.:1296.0                          3rd Qu.:30.00
##  Max.   :1749.0                          Max.   :58.00
##  trt         futime          status           risk           trt.full
##  0:197   Min.   : 0.30   Min.   :0.0000   Min.   : 6.000   Argon  : 97
##  1:197   1st Qu.:13.98   1st Qu.:0.0000   1st Qu.: 9.000   Control:197
##          Median :38.80   Median :0.0000   Median :10.000   Xenon  :100
##          Mean   :35.58   Mean   :0.3934   Mean   : 9.698
##          3rd Qu.:54.25   3rd Qu.:1.0000   3rd Qu.:11.000
##          Max.   :74.97   Max.   :1.0000   Max.   :12.000
##   eye.full              eye.type         eye.type.full       age.group
##  left :197   Left Control   : 89   Left Argon   : 56   Age 1 - 10 :116
##  right:197   Left Treatment :108   Left Control : 89   Age 11 - 19:112
##              Right Control  :108   Left Xenon   : 52   Age 20 - 29: 64
##              Right Treatment: 89   Right Argon  : 41   Age 30 - 58:102
##                                    Right Control:108
##                                    Right Xenon  : 48
```

Make Version of Data from long to wide

```
##   id laser   eye age     type   age.group futime.1 status.1 risk.1 trt.full.1
## 1  5 argon  left  28    adult Age 20 - 29    46.23        0      9      Argon
## 3 14 argon right  12 juvenile Age 11 - 19    42.50        0      8      Argon
## 5 16 xenon right   9 juvenile  Age 1 - 10    42.27        0     11      Xenon
##   eye.full.1      eye.type.1 eye.type.full.1 futime.0 status.0 risk.0
## 1       left  Left Treatment      Left Argon    46.23        0      9
## 3      right Right Treatment     Right Argon    31.30        1      6
## 5      right Right Treatment     Right Xenon    42.27        0     11
##   trt.full.0 eye.full.0    eye.type.0 eye.type.full.0
## 1    Control      right Right Control   Right Control
## 3    Control       left  Left Control    Left Control
## 5    Control       left  Left Control    Left Control
```

Summary of Data (at the patient level)

```
##        id           laser        eye           age              type
##  Min.   :   5.0   argon: 97   left :108   Min.   : 1.00   adult   : 83
##  1st Qu.: 480.0   xenon:100   right: 89   1st Qu.:10.00   juvenile:114
##  Median : 834.0                           Median :16.00
##  Mean   : 873.2                           Mean   :20.78
##  3rd Qu.:1296.0                           3rd Qu.:30.00
##  Max.   :1749.0                           Max.   :58.00
##        age.group     futime.1        status.1          risk.1
##  Age 1 - 10 :58   Min.   : 1.47   Min.   :0.0000   Min.   : 6.000
##  Age 11 - 19:56   1st Qu.:20.17   1st Qu.:0.0000   1st Qu.: 9.000
##  Age 20 - 29:32   Median :42.23   Median :0.0000   Median : 9.000
##  Age 30 - 58:51   Mean   :38.87   Mean   :0.2741   Mean   : 9.645
##                   3rd Qu.:56.80   3rd Qu.:1.0000   3rd Qu.:11.000
##                   Max.   :74.97   Max.   :1.0000   Max.   :12.000
##    trt.full.1  eye.full.1            eye.type.1       eye.type.full.1
##  Argon  : 97   left :108   Left Control   :  0   Left Argon   :56
##  Control:  0   right: 89   Left Treatment :108   Left Control : 0
```

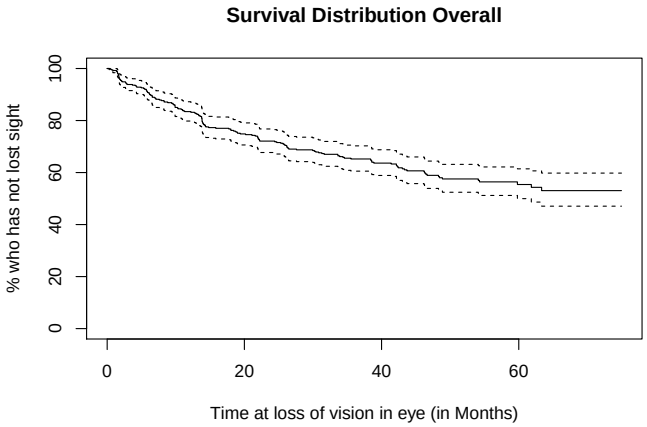
```
##  Xenon  :100               Right Control  :  0   Left Xenon   :52
##                             Right Treatment: 89   Right Argon  :41
##                                                   Right Control: 0
##                                                   Right Xenon  :48
##     futime.0        status.0          risk.0         trt.full.0  eye.full.0
##  Min.   : 0.30   Min.   :0.0000   Min.   : 6.000   Argon  :  0   left : 89
##  1st Qu.:12.20   1st Qu.:0.0000   1st Qu.: 9.000   Control:197   right:108
##  Median :32.63   Median :1.0000   Median :10.000   Xenon  :  0
##  Mean   :32.29   Mean   :0.5127   Mean   : 9.751
##  3rd Qu.:49.57   3rd Qu.:1.0000   3rd Qu.:11.000
##  Max.   :74.93   Max.   :1.0000   Max.   :12.000
##           eye.type.0       eye.type.full.0
##  Left Control   : 89   Left Argon   :  0
##  Left Treatment :  0   Left Control : 89
##  Right Control  :108   Left Xenon   :  0
##  Right Treatment:  0   Right Argon  :  0
##                        Right Control:108
##                        Right Xenon  :  0
```

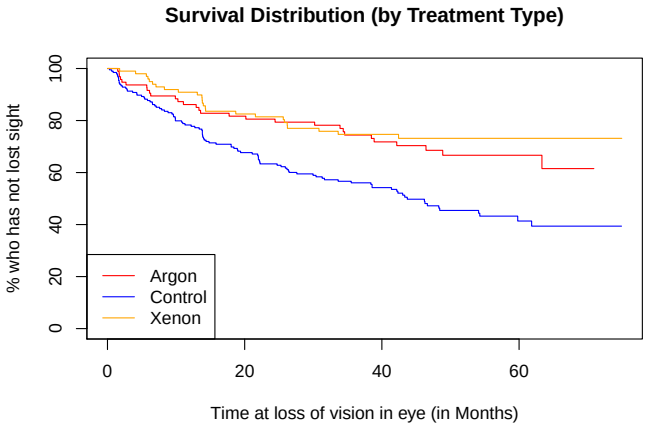
2. Data Analysis

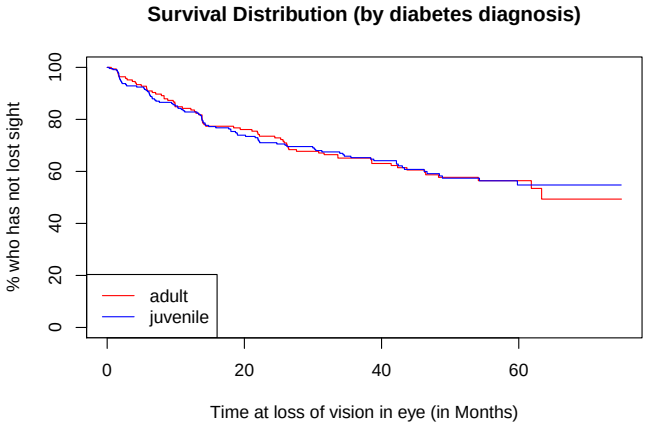
Create the survival object

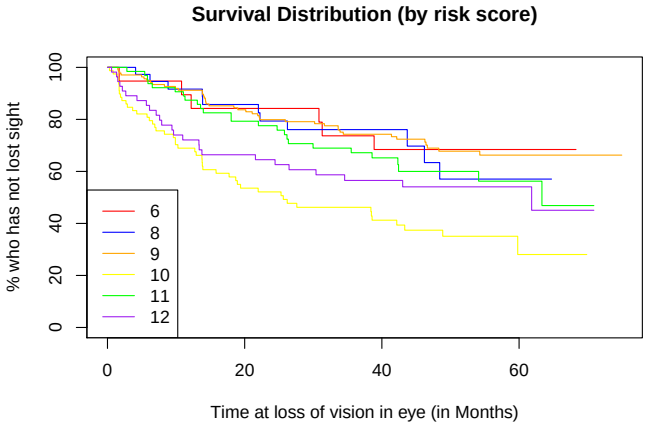
```
# Create survival object
survobj <- with(diabetic, Surv(futime, status))
```

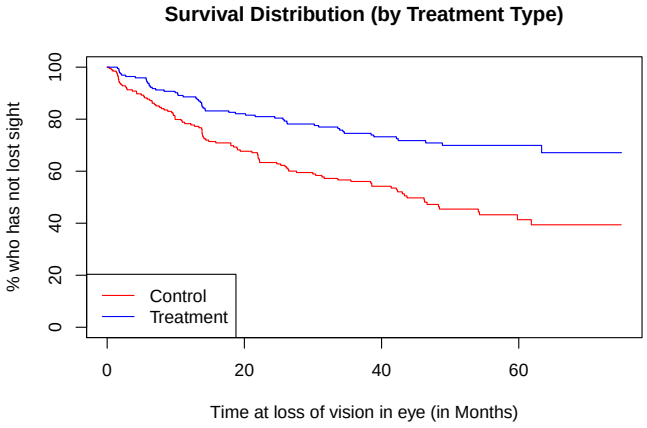
The Kaplan-Meier Survival Curve

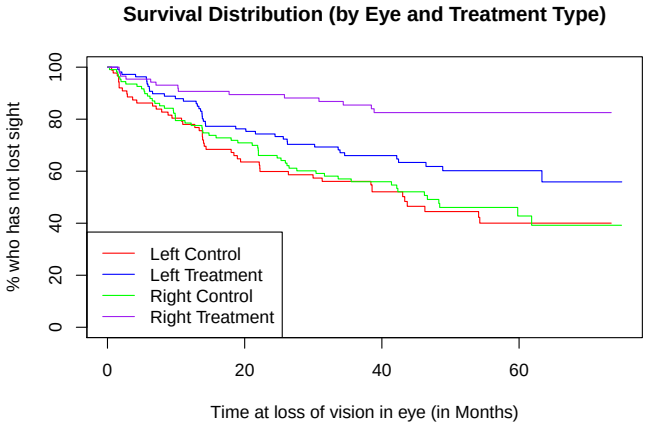


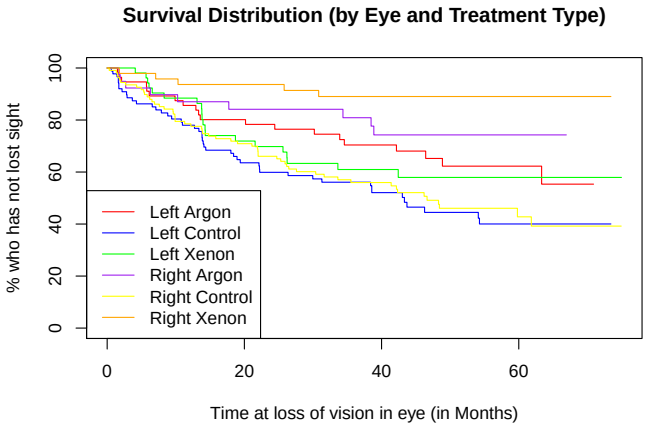


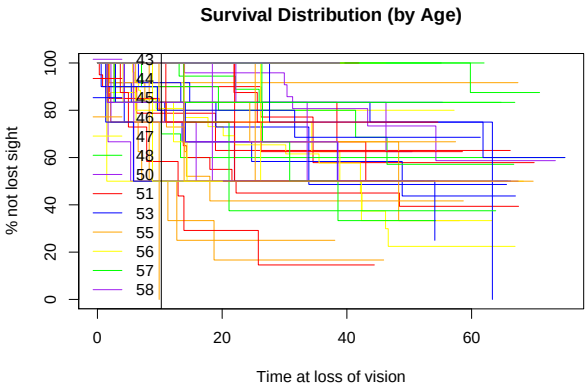


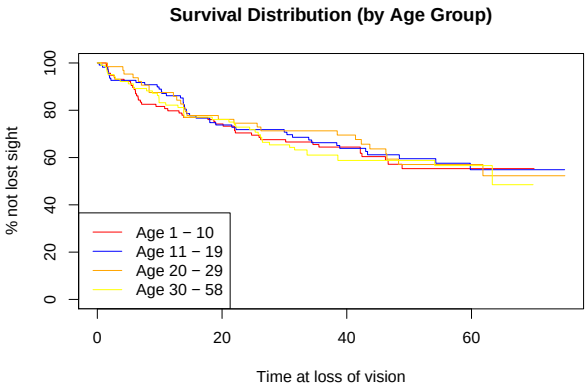


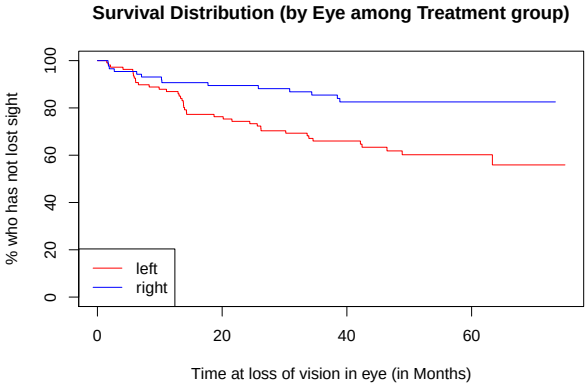












Log-Rank Tests

Testing for differences in treatment groups

```
## Call:
## survdiff(formula = survobj ~ trt, data = diabetic)
##
##         N Observed Expected (O-E)^2/E (O-E)^2/V
## trt=0 197      101     71.8      11.9      22.2
```

```
## trt=1 197       54     83.2      10.3      22.2
##
##  Chisq= 22.2  on 1 degrees of freedom, p= 2e-06
```

```
## Call:
## survdiff(formula = survobj ~ trt.full, data = diabetic)
##
##                     N Observed Expected (O-E)^2/E (O-E)^2/V
## trt.full=Argon     97       29     40.1      3.09      4.17
## trt.full=Control 197      101     71.8     11.90     22.25
## trt.full=Xenon   100       25     43.1      7.60     10.55
##
##  Chisq= 22.7  on 2 degrees of freedom, p= 1e-05
```

Testing for differences only among the treatment types

```
## Call:
## survdiff(formula = Surv(futime, status) ~ trt.full, data = diabetic.sub)
##
##                   N Observed Expected (O-E)^2/E (O-E)^2/V
## trt.full=Argon   97       29       26     0.348     0.672
## trt.full=Xenon  100       25       28     0.323     0.672
##
##  Chisq= 0.7  on 1 degrees of freedom, p= 0.4
```

Testing for differences among the age of diagnosis

```
## Call:
## survdiff(formula = survobj ~ type, data = diabetic)
##
##                  N Observed Expected (O-E)^2/E (O-E)^2/V
## type=adult     166       68     67.2   0.00988    0.0175
## type=juvenile 228       87     87.8   0.00756    0.0175
##
##  Chisq= 0  on 1 degrees of freedom, p= 0.9
```

```
## Call:
## survdiff(formula = survobj ~ age, data = diabetic)
##
##          N Observed Expected (O-E)^2/E (O-E)^2/V
## age=1   10        3    3.175  9.60e-03  9.83e-03
## age=2    4        2    1.440  2.18e-01  2.20e-01
## age=3    8        6    1.383  1.54e+01  1.56e+01
## age=4   10        2    4.267  1.20e+00  1.24e+00
## age=5   18        3    9.173  4.15e+00  4.43e+00
## age=6    6        3    1.055  3.58e+00  3.62e+00
## age=7   10        3    3.348  3.61e-02  3.70e-02
## age=8   12        6    4.720  3.47e-01  3.59e-01
## age=9   12        1    5.319  3.51e+00  3.64e+00
## age=10  26       16    9.818  3.89e+00  4.17e+00
## age=11  10        4    3.860  5.06e-03  5.21e-03
## age=12  24        6   11.244  2.45e+00  2.64e+00
```

```
## age=13 20       12    7.078  3.42e+00  3.59e+00
## age=14 12        4    4.462  4.79e-02  4.95e-02
## age=15 14        6    3.643  1.53e+00  1.57e+00
## age=16 10        4    3.048  2.97e-01  3.04e-01
## age=17 12        1    7.006  5.15e+00  5.44e+00
## age=18  4        2    1.145  6.39e-01  6.45e-01
## age=19  6        3    2.630  5.20e-02  5.30e-02
## age=20 12        4    6.142  7.47e-01  7.81e-01
## age=21  6        3    2.274  2.32e-01  2.35e-01
## age=22  6        4    2.163  1.56e+00  1.58e+00
## age=23 10        4    4.798  1.33e-01  1.37e-01
## age=24  6        2    2.599  1.38e-01  1.41e-01
## age=25  8        3    3.704  1.34e-01  1.37e-01
## age=26  6        3    2.273  2.33e-01  2.37e-01
## age=27  4        3    0.889  5.01e+00  5.06e+00
## age=28  4        0    1.347  1.35e+00  1.36e+00
## age=29  2        0    1.217  1.22e+00  1.23e+00
## age=30  6        3    2.761  2.07e-02  2.11e-02
## age=32  6        0    2.707  2.71e+00  2.77e+00
## age=33  6        1    2.692  1.06e+00  1.08e+00
## age=34  2        1    0.890  1.37e-02  1.38e-02
## age=35  2        1    0.986  2.07e-04  2.09e-04
## age=36  6        1    3.321  1.62e+00  1.66e+00
## age=37  2        1    0.645  1.95e-01  1.96e-01
## age=38  2        1    0.843  2.93e-02  2.95e-02
## age=39  4        2    2.109  5.59e-03  5.68e-03
## age=40  4        3    0.510  1.22e+01  1.23e+01
## age=41  2        1    0.272  1.95e+00  1.96e+00
## age=42  4        2    1.433  2.24e-01  2.27e-01
## age=43  2        1    0.575  3.14e-01  3.17e-01
## age=44  8        6    1.606  1.20e+01  1.22e+01
## age=45 10        3    3.976  2.40e-01  2.47e-01
## age=46  6        2    2.478  9.22e-02  9.39e-02
## age=47  2        0    0.902  9.02e-01  9.09e-01
## age=48  6        4    2.351  1.16e+00  1.18e+00
## age=50  6        3    2.467  1.15e-01  1.17e-01
## age=51  4        1    1.705  2.92e-01  2.95e-01
## age=53  4        3    1.223  2.58e+00  2.61e+00
## age=55  2        1    0.865  2.10e-02  2.12e-02
## age=56  2        1    0.430  7.57e-01  7.62e-01
## age=57  2        0    1.142  1.14e+00  1.15e+00
## age=58  2        0    0.892  8.92e-01  8.99e-01
##
##  Chisq= 99.6  on 53 degrees of freedom, p= 1e-04
```

Testing for differences among risk score

```
## Call:
## survdiff(formula = survobj ~ risk, data = diabetic)
##
##           N Observed Expected (O-E)^2/E (O-E)^2/V
## risk=6   20        6     8.68    0.8285    0.8791
## risk=8   37       11    14.73    0.9467    1.0480
```

```
## risk=9  139       41    61.67    6.9299   11.5767
## risk=10  79       47    23.81   22.5717   26.8303
## risk=11  64       25    26.33    0.0668    0.0806
## risk=12  55       25    19.77    1.3842    1.5887
##
##  Chisq= 33  on 5 degrees of freedom, p= 4e-06
```

Testing for differences among the treated eye (left and right)

```
## Call:
## survdiff(formula = Surv(futime, status) ~ eye, data = diabetic)
##
##             N Observed Expected (O-E)^2/E (O-E)^2/V
## eye=left  216       95     84.7      1.26      2.79
## eye=right 178       60     70.3      1.52      2.79
##
##  Chisq= 2.8  on 1 degrees of freedom, p= 0.09
```

```
## Call:
## survdiff(formula = Surv(futime, status) ~ eye.full, data = diabetic)
##
##                  N Observed Expected (O-E)^2/E (O-E)^2/V
## eye.full=left  197       86     75.2      1.56      3.03
## eye.full=right 197       69     79.8      1.47      3.03
##
##  Chisq= 3  on 1 degrees of freedom, p= 0.08
```

```
## Call:
## survdiff(formula = Surv(futime, status) ~ eye.type, data = diabetic)
##
##                            N Observed Expected (O-E)^2/E (O-E)^2/V
## eye.type=Left Control     89       46     31.1     7.089     8.891
## eye.type=Left Treatment  108       40     44.0     0.369     0.516
## eye.type=Right Control   108       55     40.6     5.083     6.902
## eye.type=Right Treatment  89       14     39.2    16.199    21.764
##
##  Chisq= 28.9  on 3 degrees of freedom, p= 2e-06
```

```
## Call:
## survdiff(formula = Surv(futime, status) ~ eye.type.full, data = diabetic)
##
##                               N Observed Expected (O-E)^2/E (O-E)^2/V
## eye.type.full=Left Argon     56       20     23.9  6.39e-01  7.57e-01
## eye.type.full=Left Control   89       46     31.1  7.09e+00  8.89e+00
## eye.type.full=Left Xenon     52       20     20.1  7.35e-04  8.46e-04
## eye.type.full=Right Argon    41        9     16.2  3.21e+00  3.59e+00
## eye.type.full=Right Control 108       55     40.6  5.08e+00  6.90e+00
## eye.type.full=Right Xenon    48        5     23.0  1.41e+01  1.66e+01
##
##  Chisq= 30.2  on 5 degrees of freedom, p= 1e-05
```

Models

Simple Cox Model

```
diabetic$trt.full = relevel(diabetic$trt.full, ref = "Control")
cox.model <- coxph(Surv(futime, status) ~ trt.full + eye.full + age + type + risk, data=diabetic)
summary(cox.model)
```

```
## Call:
## coxph(formula = Surv(futime, status) ~ trt.full + eye.full +
##     age + type + risk, data = diabetic)
##
##   n= 394, number of events= 155
##
##                     coef exp(coef)  se(coef)      z Pr(>|z|)
## trt.fullArgon -0.737974  0.478081  0.213350 -3.459 0.000542 ***
## trt.fullXenon -0.904028  0.404935  0.223665 -4.042  5.3e-05 ***
## eye.fullright -0.325972  0.721825  0.164065 -1.987 0.046940 *
## age            0.007788  1.007819  0.009713  0.802 0.422623
## typejuvenile   0.129157  1.137869  0.291374  0.443 0.657571
## risk           0.143586  1.154406  0.055465  2.589 0.009632 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## trt.fullArgon    0.4781     2.0917    0.3147    0.7263
## trt.fullXenon    0.4049     2.4695    0.2612    0.6277
## eye.fullright    0.7218     1.3854    0.5233    0.9956
## age              1.0078     0.9922    0.9888    1.0272
## typejuvenile     1.1379     0.8788    0.6428    2.0142
## risk             1.1544     0.8662    1.0355    1.2870
##
## Concordance= 0.634  (se = 0.023 )
## Likelihood ratio test= 35.02  on 6 df,   p=4e-06
## Wald test            = 33.31  on 6 df,   p=9e-06
## Score (logrank) test = 34.48  on 6 df,   p=5e-06
```

Cox Model with Frailty Term

Interpretation:

- The estimated hazard for an eye with the Argon laser treatment is 0.3656 times less than an eye in the control. In other words,, with all features held fixed, argon eyes have 0.3656 time less chance of losing eyesight than control, at any point in time.

```
frail.model <- coxph(Surv(futime, status) ~ trt.full + eye.full + age + risk + frailty(id), data=diabeti
summary(frail.model)
```

```
## Call:
## coxph(formula = Surv(futime, status) ~ trt.full + eye.full +
```

```
##     age + risk + frailty(id), data = diabetic)
##
##   n= 394, number of events= 155
##
##                coef     se(coef) se2      Chisq  DF    p
## trt.fullArgon -1.00633 0.237443 0.224119  17.96  1.00 2.3e-05
## trt.fullXenon -1.03222 0.236807 0.229055  19.00  1.00 1.3e-05
## eye.fullright -0.47241 0.178240 0.171477   7.02  1.00 8.0e-03
## age            0.00538 0.007721 0.005689   0.49  1.00 4.9e-01
## risk           0.16391 0.071503 0.060383   5.25  1.00 2.2e-02
## frailty(id)                              126.64 89.59 6.1e-03
##
##                exp(coef) exp(-coef) lower .95 upper .95
## trt.fullArgon     0.3656     2.7355    0.2295    0.5822
## trt.fullXenon     0.3562     2.8073    0.2239    0.5666
## eye.fullright     0.6235     1.6038    0.4397    0.8842
## age               1.0054     0.9946    0.9903    1.0207
## risk              1.1781     0.8488    1.0240    1.3553
##
## Iterations: 6 outer, 32 Newton-Raphson
##      Variance of random effect= 0.9562888   I-likelihood = -844
## Degrees of freedom for terms=  1.8  0.9  0.5  0.7 89.6
## Concordance= 0.859  (se = 0.859 )
## Likelihood ratio test= 228.3  on 93.58 df,   p=3e-13
```

```
estimates <- cbind(Estimate = coef(frail.model), confint(frail.model))
round(exp(estimates), 2)
```

```
##                Estimate 2.5 % 97.5 %
## trt.fullArgon      0.37  0.23   0.58
## trt.fullXenon      0.36  0.22   0.57
## eye.fullright      0.62  0.44   0.88
## age                1.01  0.99   1.02
## risk               1.18  1.02   1.36
```

Frailty Model using different R Library

```
coxme(Surv(futime, status) ~ trt.full + eye.full + age + risk + (1 | id), data=diabetic)
```

```
## Cox mixed-effects model fit by maximum likelihood
##   Data: diabetic
##   events, n = 155, 394
##   Iterations= 10 54
##                     NULL Integrated    Fitted
## Log-likelihood -867.9858  -844.1232 -753.3601
##
##                    Chisq    df          p   AIC     BIC
## Integrated loglik  47.73  6.00 1.3408e-08 35.73   17.46
##  Penalized loglik 229.25 82.92 1.2212e-15 63.41 -188.94
##
## Model:  Surv(futime, status) ~ trt.full + eye.full + age + risk + (1 |      id)
```

```
## Fixed coefficients
##                         coef exp(coef)    se(coef)     z       p
## trt.fullArgon -0.994443184 0.3699294 0.236553446 -4.20 2.6e-05
## trt.fullXenon -1.032165265 0.3562348 0.236421195 -4.37 1.3e-05
## eye.fullright -0.468335406 0.6260435 0.176581767 -2.65 8.0e-03
## age            0.005343259 1.0053576 0.007305943  0.73 4.6e-01
## risk           0.160415840 1.1739990 0.068710626  2.33 2.0e-02
##
## Random effects
##  Group Variable  Std Dev   Variance
##  id    Intercept 0.9563375 0.9145815
```