Modelling exemplification

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Aim

The aim of this document is to clarify the modelling assumptions used in the simulations for defining the operational characteristics of ProBio. I first describe the parametric assumptions and use fictitious data for exemplifying the updating evaluation of the trial.

Modelling assumption

We are going to use Bayesian methods for survival analysis. In a Bayesian framework, a parametric distribution is often selected for modelling a time to event variable, in our case progression free survival (PFS).

A Weibull distribution is typically adopted in many bio-medical contexts, given its flexibility in describing several different shapes and phenomena. A Weibull distribution can be parameterized in terms of a scale (λ) and shape (k) parameter is such a way that it density function assumes the following form:

$$T \sim \text{Weibull}(\lambda, k)$$

$$f(t; \lambda, k) = \lambda k t^{k-1} \exp(-\lambda t^k)$$

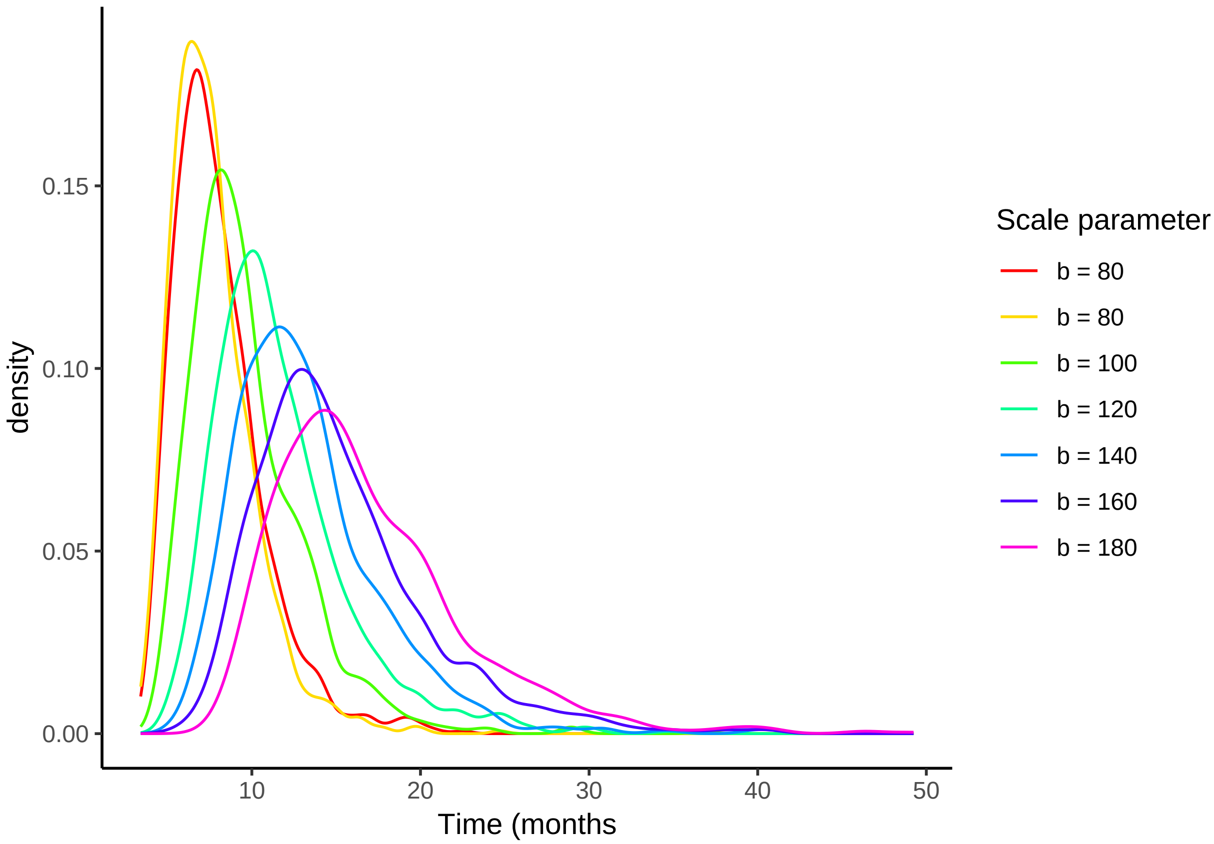
The mean in the previous parametrization is $\lambda^{-\frac{1}{k}} \Gamma(1 + \frac{1}{k})$.

In a Bayesian perspective, we are considering the parameters of interest as random variables rather than fixed values. In particular, we are going to assume a distribution for the scale parameter while fixing the shape parameter at 1.05, as estimated in an international study on similar patients. We adopt a gamma distribution for the scale parameter as it is a conjugate model for the Weibull distribution:

$$\lambda \sim \text{Gamma}(a, b)$$
$$f(\lambda; a, b) = \frac{b^a \lambda^{a-1} \exp(-b\lambda)}{\Gamma(a)}$$

As a priori parameter we are going to use $a = 10$ and $b = 80$ as hyperparameters, that corresponds approximately to the information of 10 patient with a mean $E[\lambda] = \frac{a}{b} = 1/8 = 0.125$, which then gives a mean PFS time equal to $E[T] = 0.125^{-1/1.05} \Gamma(1 + \frac{1}{1.05}) = 7.1$.

Let's compare how the distribution of PFS times changes as the b hyperparameter increases from 80 to 180:



We can compare the distributions by comparing the respective means.

```
       b mean gamma mean time
[1,]  80 0.12500000  7.106618
[2,] 100 0.10000000  8.789380
[3,] 120 0.08333333 10.456082
[4,] 140 0.07142857 12.109545
[5,] 160 0.06250000 13.751758
[6,] 180 0.05555556 15.384200
```

In addition, we might compare how much is the evidence that the distributions differ from each other. For example, what is the probability that then mean time of a Weibull distribution where the λ parameter has a gamma distribution with $a = 10$ and $b = 140$ is greater than the mean of a similar distribution but with $b = 80$? This can be computed using Monte Carlo simulations

```
       b mean gamma mean time prob of superiority
[1,]  80 0.12500000  7.106618               0.459
[2,] 100 0.10000000  8.789380               0.659
[3,] 120 0.08333333 10.456082               0.794
[4,] 140 0.07142857 12.109545               0.863
[5,] 160 0.06250000 13.751758               0.927
[6,] 180 0.05555556 15.384200               0.954
```

Exemplification clinical trial

Let's use a fictitious example data set to exemplify how the hyperparameters are update throughout the trial, how we can decide to ealier stop the trial.

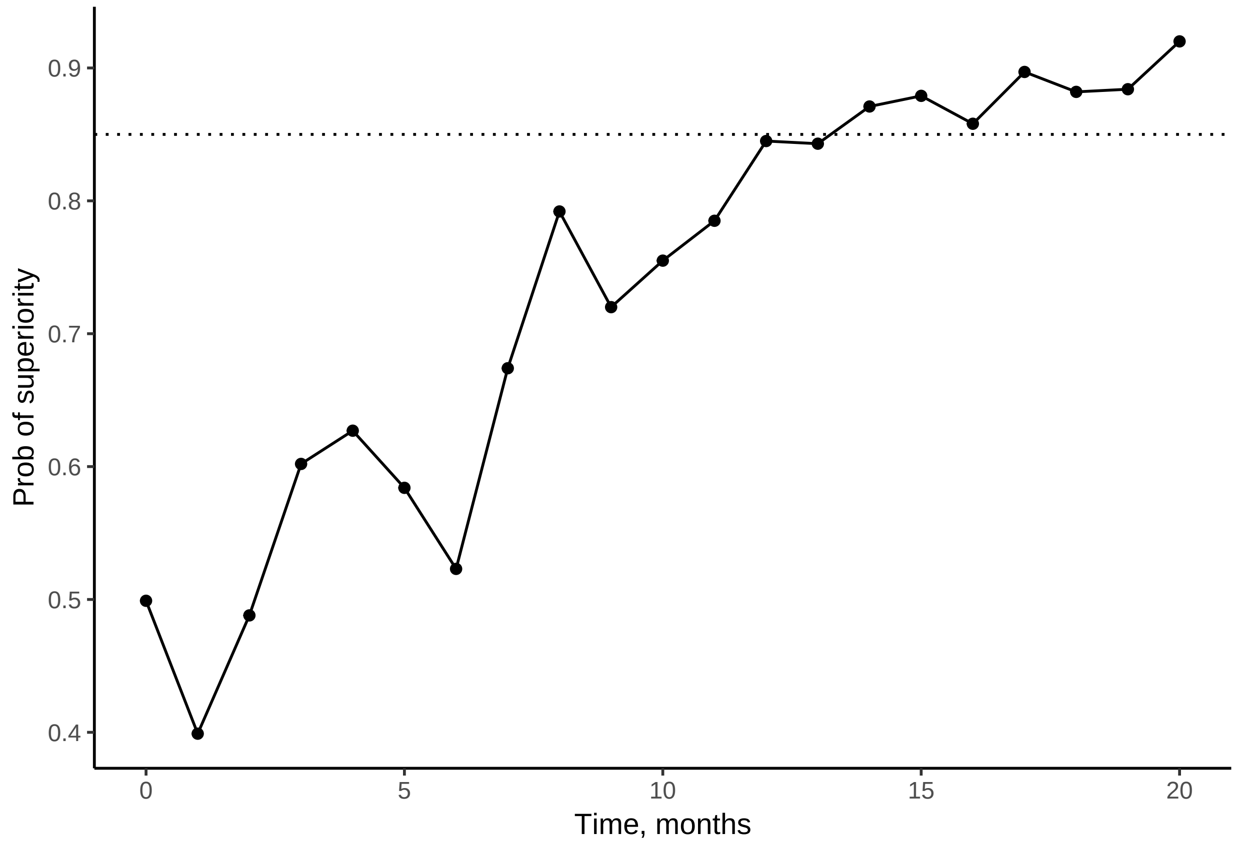
We consider one active treatment being compared vs a control group. Each group consists of 25 patients whose PFS time has been recorded in the first 20 months. The PFS times for those men still alive at the end of the follow-up are marked with a "+" in the table below

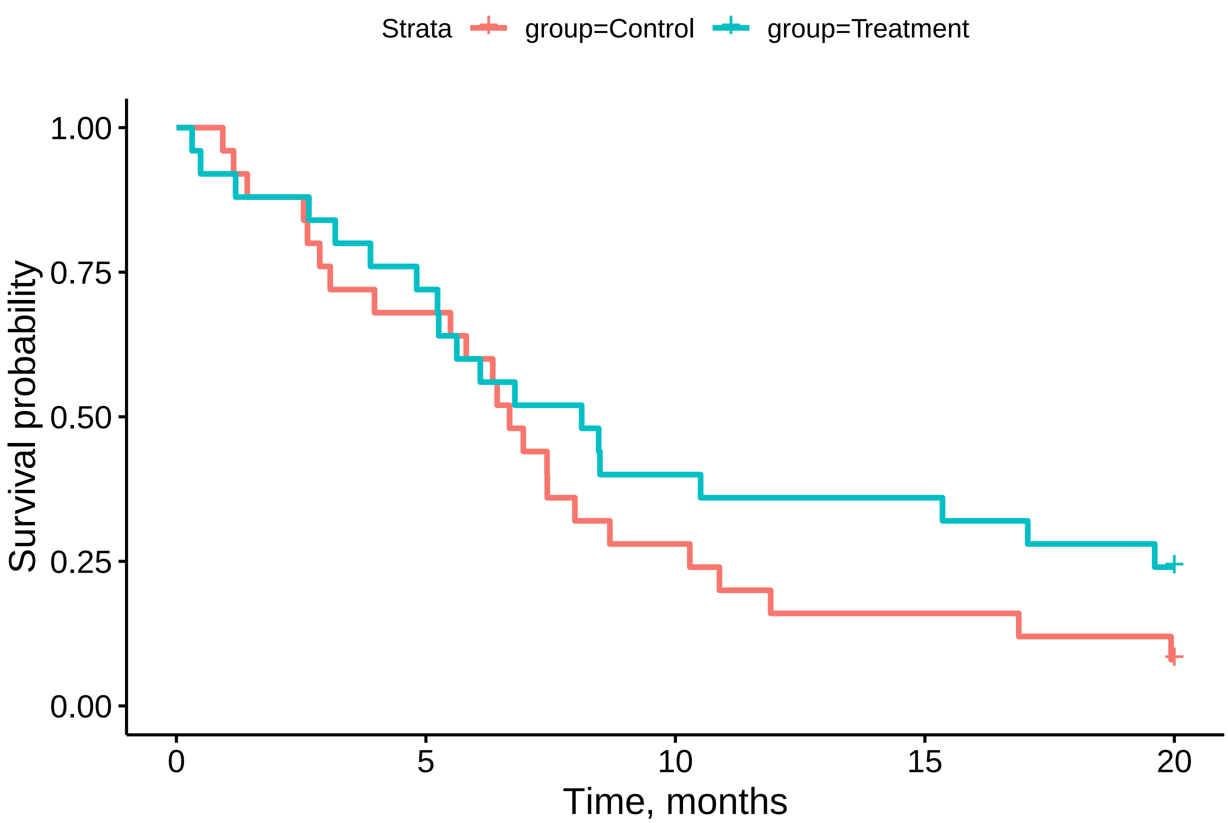
Control	Treatment
2.55, 6.43, 2.87, 6.68, 11.91, 6.95, 3.08, 7.43, 10.29, 6.34, 7.99, 19.93, 1.15, 20.00+, 7.43, 5.49, 8.69, 0.93, 2.63, 10.88, 16.88, 5.81, 1.42, 3.97, 20.00+	8.49, 20.00+, 3.18, 19.61, 20.00+, 15.35, 17.06, 20.00+, 10.51, 3.89, 20.00+, 8.12, 6.09, 20.00+, 2.66, 8.46, 0.48, 4.81, 5.26, 6.78, 5.62, 1.19, 20.00+, 0.31, 5.23

The hyperparameters of the Gamma distibution are updated monthly. In particula the hyperparameter a is updated with the number of progressions while b with the amount of time the patients stayed in the trial. For example, in the firs month there have been 1 and 2 progressions in the control and treatment groups. After the first month $a = 10 + 1$ in the control group, while $a = 10 + 2$ in the treatment group. Similarly, the observed person times (elevated to the power of 1.05) in the first month were 24.93 and 23.8, so that $b = 80 + 24.93$ and $b = 80 + 23.76$ in the control and treatment group. Given the hyperparameters it is possible to compare if the treatment is superior to control group.

The same steps can be repeated monthly:

	Control						Treatment						
month	a	b	d	PT	mu gam	mu time	a	b	d	PT	mu gam	mu time	p
0	10	80.0	1	24.925	0.1250	7.107	10	80.0	2	23.763	0.1250	7.107	0.499
1	11	104.9	2	22.534	0.1048	8.403	12	103.8	1	22.171	0.1156	7.653	0.399
2	13	129.1	3	21.011	0.1007	8.730	13	127.5	1	21.642	0.1020	8.629	0.488
3	16	152.2	2	18.041	0.1051	8.381	14	151.3	2	20.051	0.0925	9.464	0.602
4	18	172.4	0	17.000	0.1044	8.434	16	173.7	1	18.806	0.0921	9.507	0.627
5	18	191.6	2	16.275	0.0939	9.329	17	195.0	3	16.061	0.0872	10.018	0.584
6	20	210.3	4	13.346	0.0951	9.218	20	213.4	2	13.854	0.0937	9.351	0.523
7	24	225.7	3	9.810	0.1063	8.290	22	229.4	0	13.000	0.0959	9.148	0.674
8	27	237.1	1	7.674	0.1139	7.767	22	244.5	3	11.027	0.0900	9.721	0.792
9	28	246.1	0	7.000	0.1138	7.773	25	257.5	0	10.000	0.0971	9.040	0.720
10	28	254.3	2	6.149	0.1101	8.020	25	269.2	1	9.489	0.0929	9.432	0.755
11	30	261.6	1	4.905	0.1147	7.715	26	280.5	0	9.000	0.0927	9.447	0.785
12	31	267.4	0	4.000	0.1159	7.636	26	291.1	0	9.000	0.0893	9.789	0.845
13	31	272.2	0	4.000	0.1139	7.766	26	301.9	0	9.000	0.0861	10.132	0.843
14	31	277.0	0	4.000	0.1119	7.896	26	312.6	0	9.000	0.0832	10.476	0.871
15	31	281.8	0	4.000	0.1100	8.026	26	323.4	1	8.335	0.0804	10.820	0.879
16	31	286.6	1	3.877	0.1082	8.157	27	333.5	0	8.000	0.0810	10.747	0.858
17	32	291.3	0	3.000	0.1099	8.037	27	343.1	1	7.053	0.0787	11.043	0.897
18	32	294.9	0	3.000	0.1085	8.133	28	351.7	0	7.000	0.0796	10.921	0.882
19	32	298.6	1	2.931	0.1072	8.228	28	360.2	1	6.592	0.0777	11.172	0.884
20	33	302.2	0	0.000	0.1092	8.082	29	368.2	0	0.000	0.0788	11.035	0.920


Prob of superiority
0.4
0.5
0.6
0.7
0.8
0.9
0
5
10
15
20
Time, months


Strata
group=Control
group=Treatment
Survival probability
0.00
0.25
0.50
0.75
1.00
0
5
10
15
20
Time, months