MORSE
Health Technology Assessment Group

Roche

Predicting long term survival using non-parametric bayesian methods: the melanoma case

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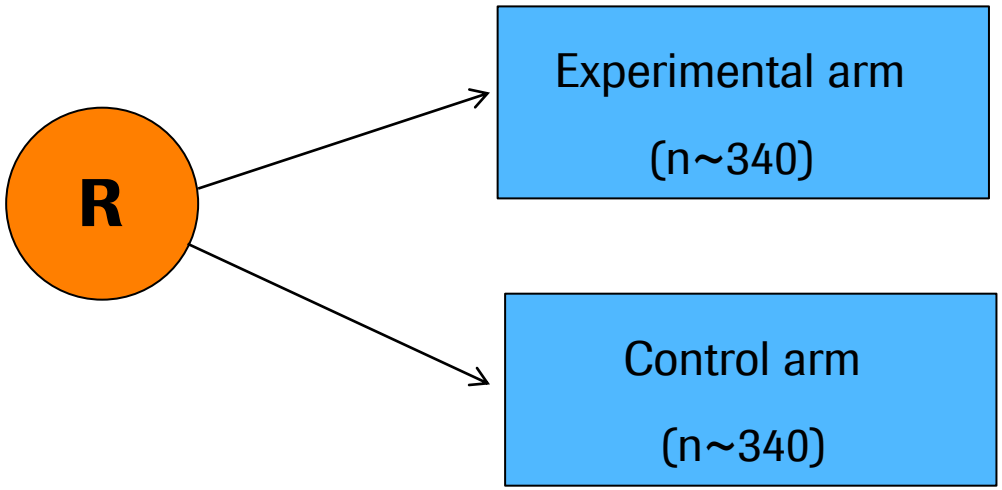
BBS - EFSPI 2015 – June 23, 2015

Melanoma

- Type of skin cancer
- Less common than other skin cancers
- More dangerous if it is not treated early
- Causes 75% of deaths related to skin cancer

Clinical trial

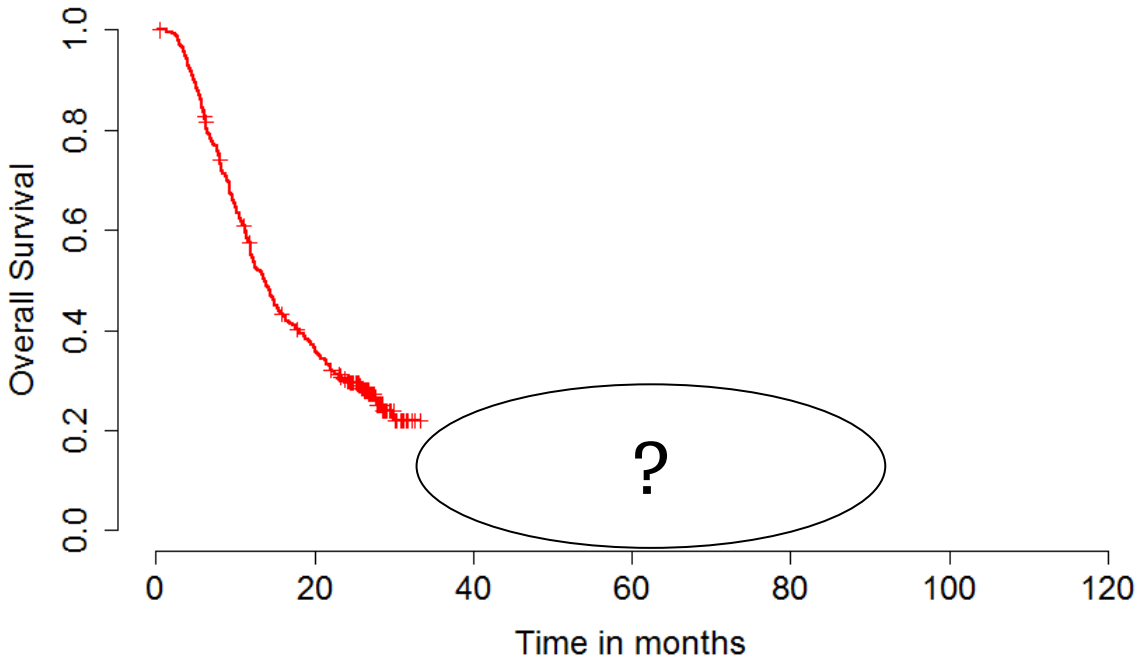


For the purpose of this application:

- Consider overall survival endpoint. Focus on active treatment arm due to high percentage of “crossover” after early data cut
- 94% of patients in trial were stage IV → 5-year survival rates of 15%-20%

A key question in Health Technology Assessment is:

How to extrapolate survival data from a clinical trial?



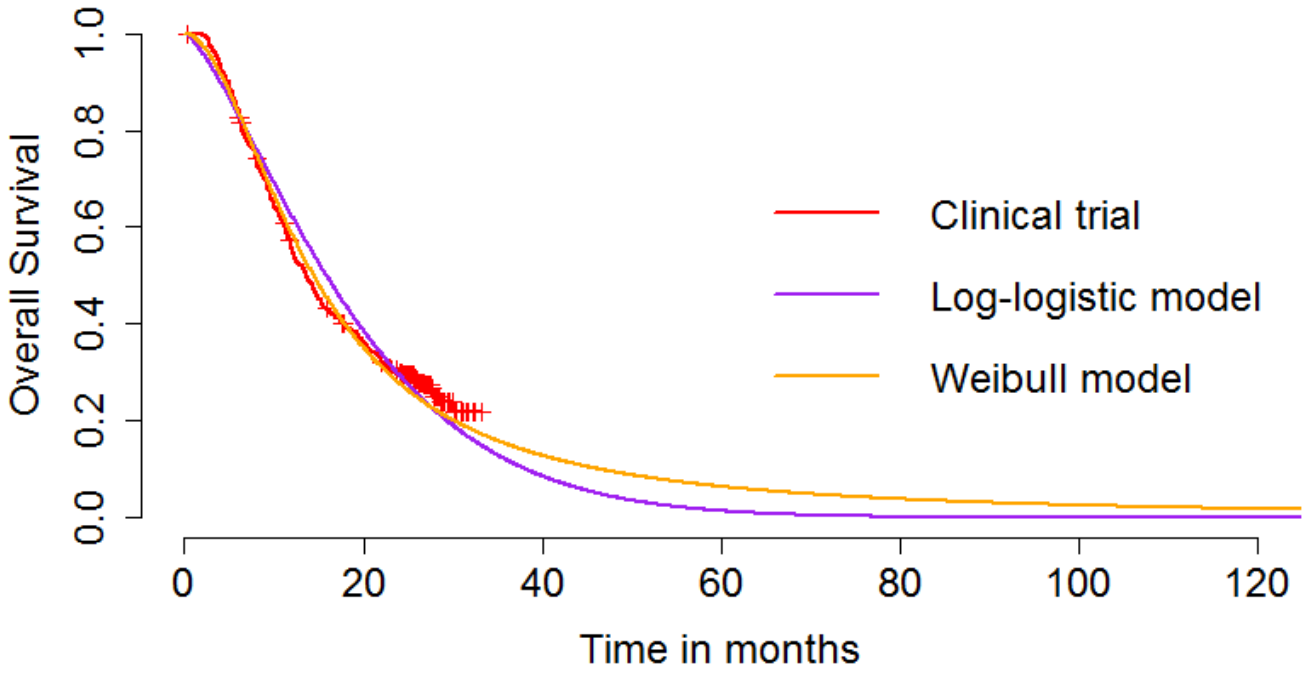
Characteristics of a clinical trial data

Ideal Conditions

- Randomization
- Blinding
- Clean database

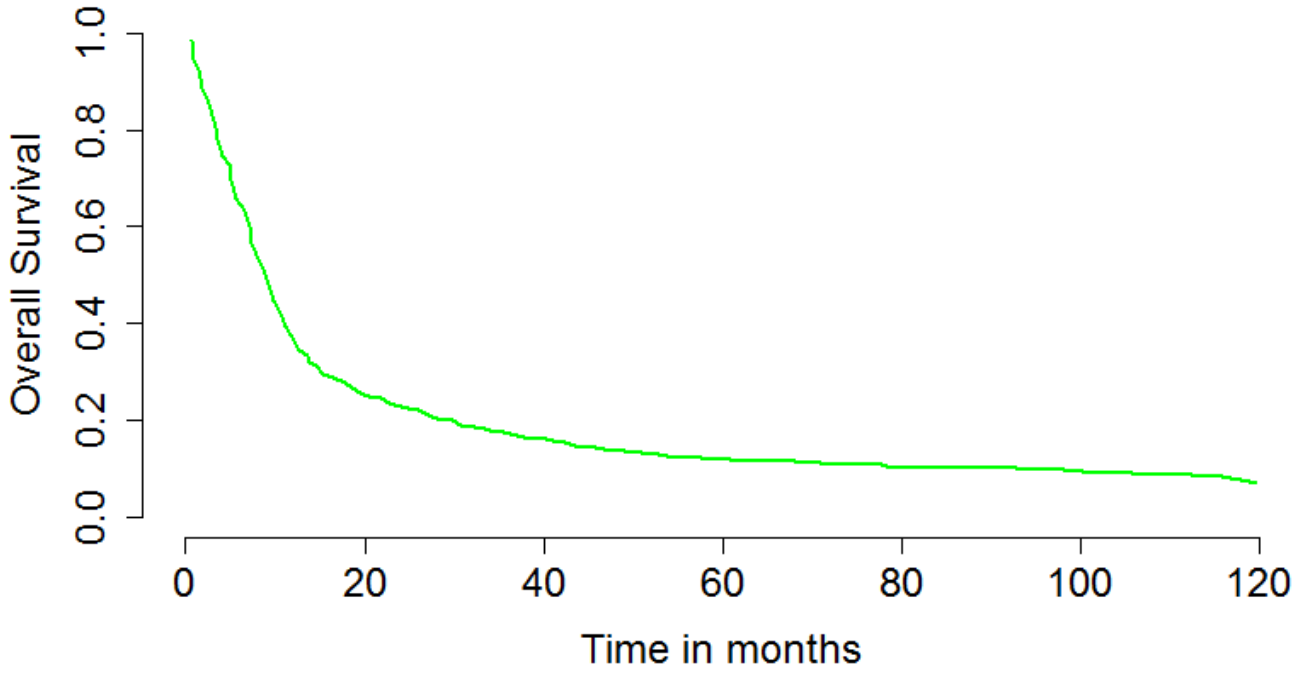
- May not reflect real practice
- Limited follow up

One way to answer is to apply parametric extrapolation



We should assess plausibility of our extrapolations. Latimer (2013).

In fact we can consider registry data:



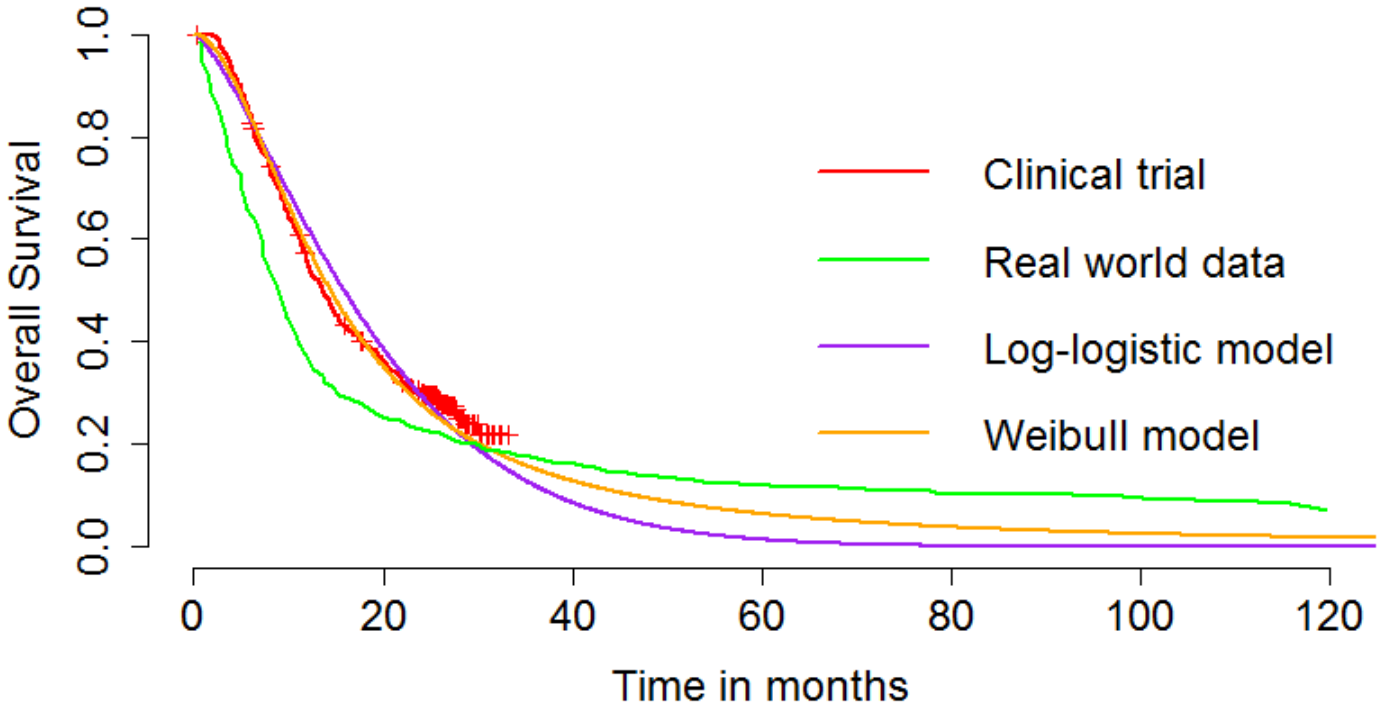
Patients with at least 5 years of follow up from a registry published in Xing et al (2010).

Characteristics of a real world data

- It may reflect clinical practice
- Longer follow up

- May be limited to one country or one region
- Incomplete information about patients

What happen when we compare our parametric extrapolation with the real world data



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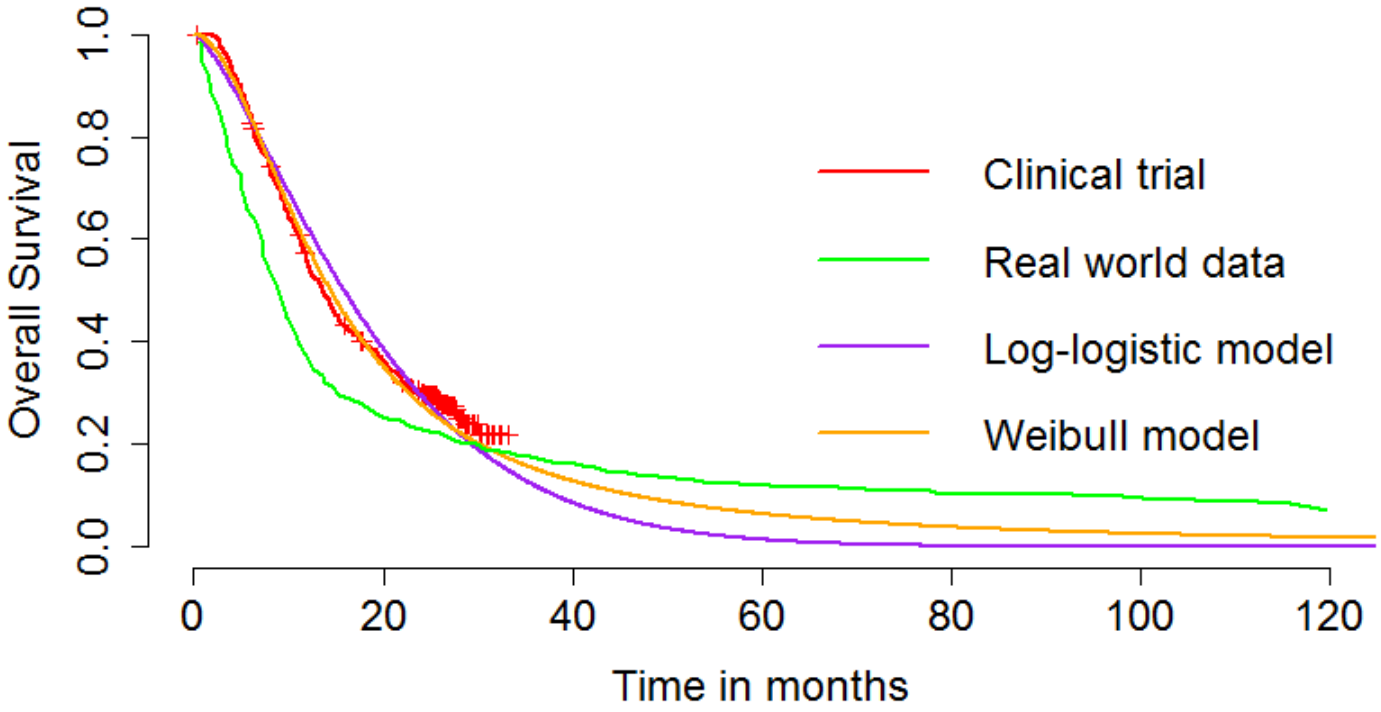
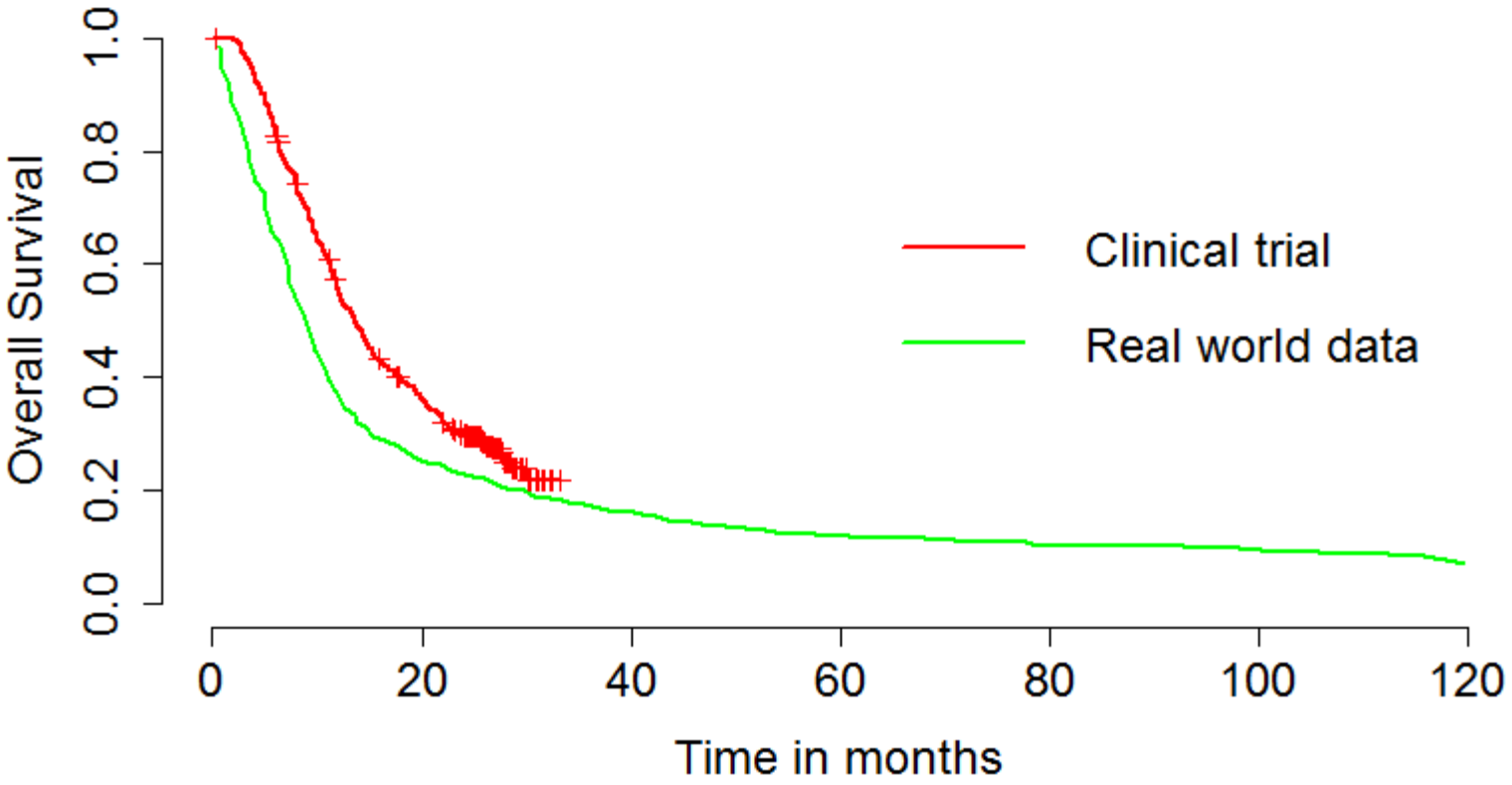


The problem is all the parametric extrapolations we perform lead to a heavy underestimation of survival rate

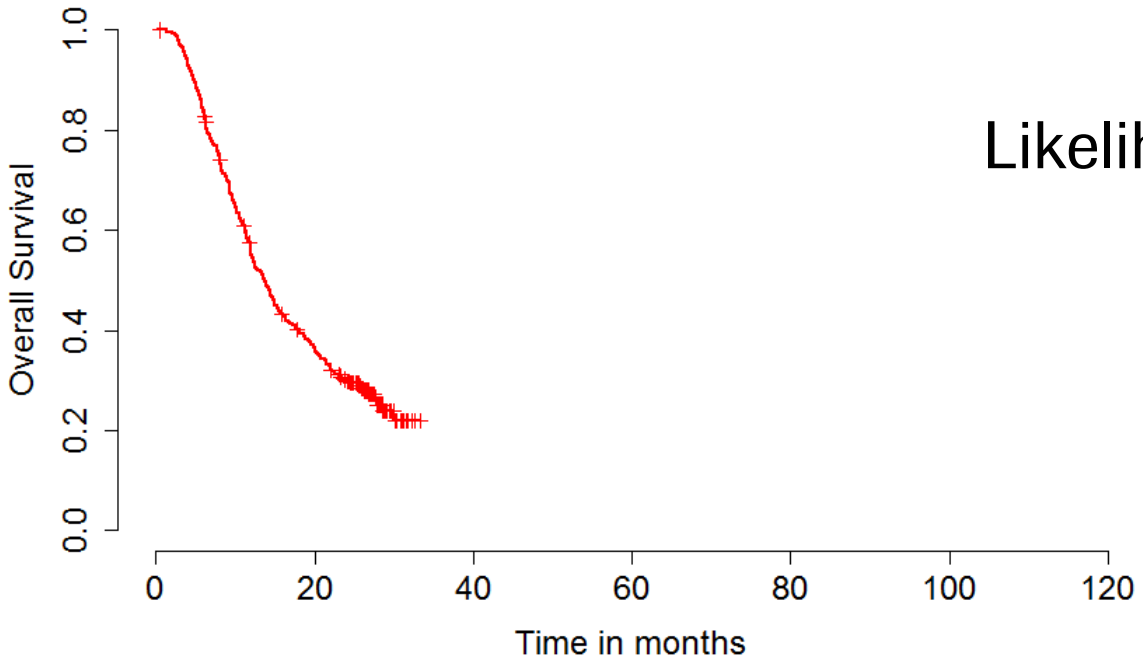
Another option is:

Combine the two sources of information we have



The clinical trial data has:

- “Short” follow up relatively to the time horizon considered in the health economics models
- “A lot” of censored observations specially in the tail

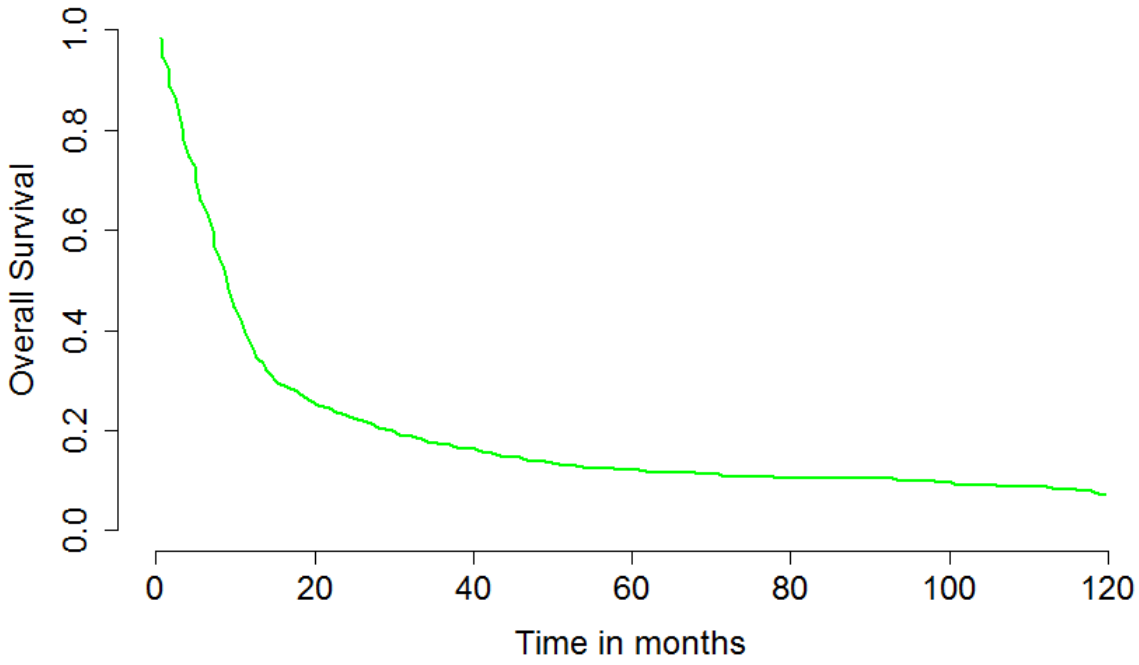


Likelihood

We have some previous knowledge:

- Real world data
- Longer follow up clinical trial

Prior



We can combine them using Bayesian estimation

$$\text{Posterior} \propto \text{prior} * \text{likelihood}$$

Prior = observational data

Likelihood = available (trial) data

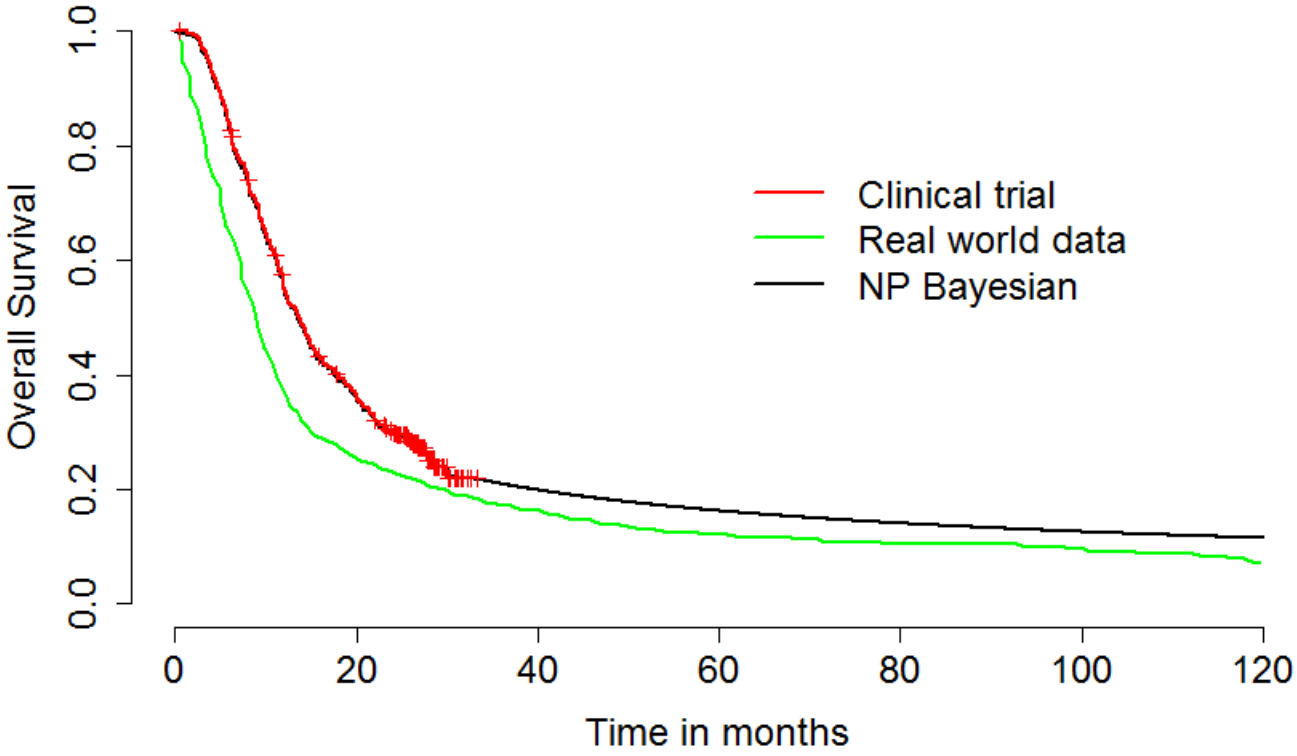
We use a Bayesian nonparametric estimation

- The prior is based on a Dirichlet process.
- For survival analysis previous work based on Dirichlet processes was proposed by Ferguson and Phadia (1979) and Susarla and Van Ryzin (1976).
- We assume the survival function follows a Dirichlet distribution with certain parameter.
- The form of the $S(t)=cS_0(t)$
- $S_0(t)$ is our prior guess at the survival function
- c is a measure of how much weight we put on our prior guess (larger value of c lead to smoother function)

Non parametric Bayesian estimator

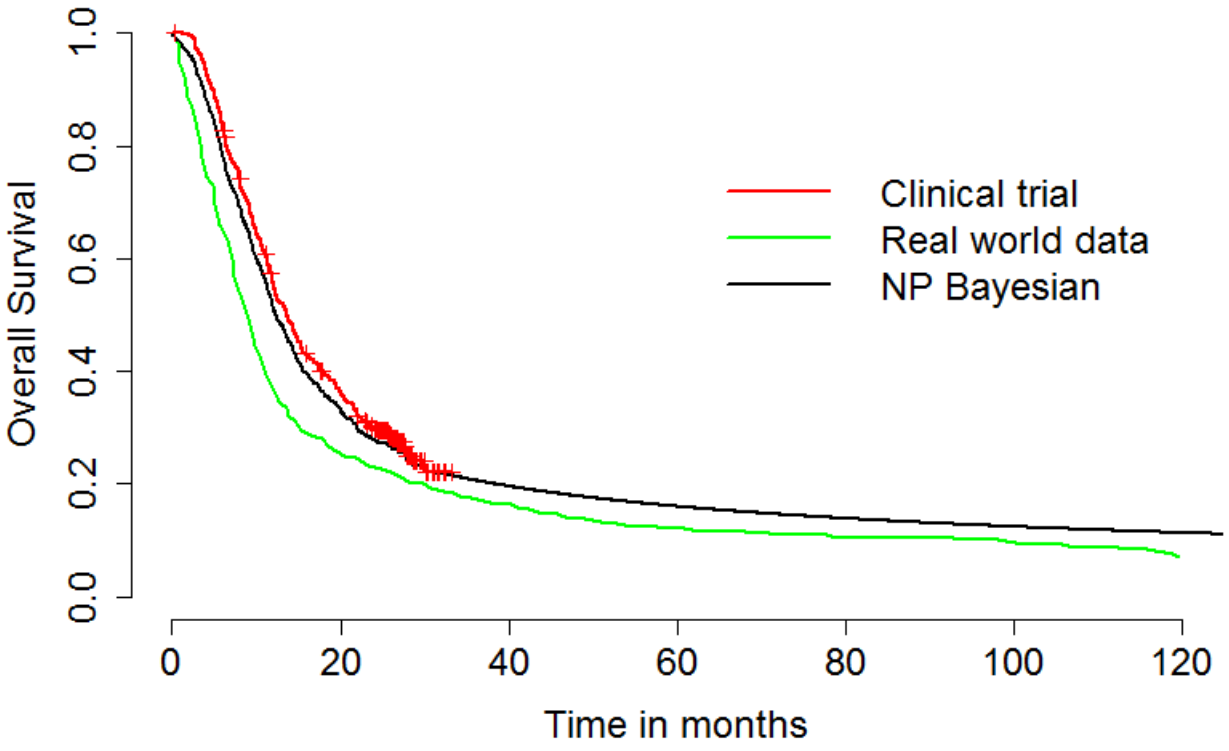
- Continuous function between two event times
- Coincides with the Kaplan Meier estimation for big sample size
- Is driven by the prior information for small sample size
- Takes into account the censoring and the event times

Nonparametric Bayesian estimation c=10



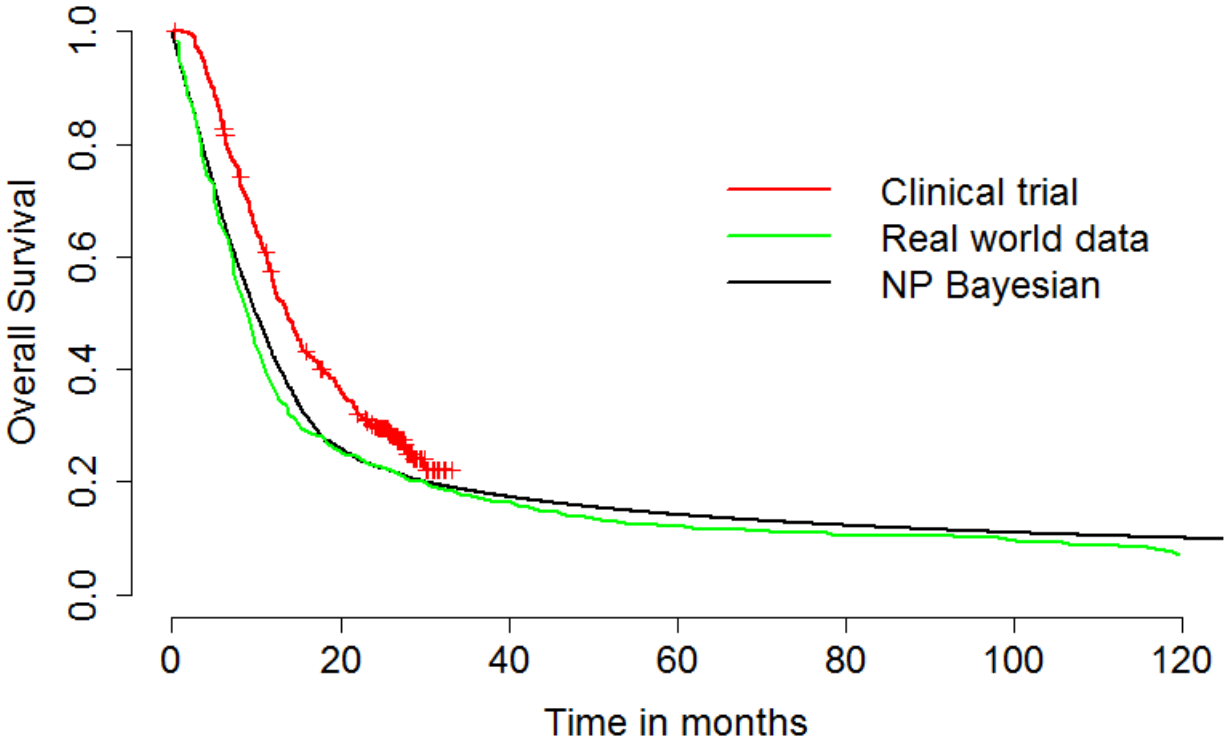
It overlaps with Kaplan Meier estimate while there is clinical trial available, when c equal to 10

Nonparametric Bayesian estimation c=100



Slightly under the Kaplan Meier from the clinical trial when c is equal to 100

Nonparametric Bayesian estimation c=1000



It overlaps with the Kaplan Meier from the real world data when c is equal to 1000

How to extrapolate survival data from a clinical trial?

- Combining clinical trial data with real world data
- This is possible in the Bayesian framework
- Several sensitivity analyses should be carried out

Some advantages of the Bayesian nonparametric estimation

- It is defined for all the time points (not only for the follow up trial)
- It allows combination between prior information and clinical trial data
- If we assume a Dirichlet process $S_0(t)$ is an exponential distribution
- Assuming a squared error loss function we have a conjugate prior, therefore we have a close form solution for the posterior distribution.

Statistical background

Using a squared-error loss function:

$$L(S, \hat{S}) = \int_0^\infty \left[\hat{S}(t) - S(t)\right]^2 dw(t),$$

where $w(t)$ is a weight function.

There are two classes of prior distribution that lead to a closed form estimates of the survival functions.

- Prior distribution for the survival function.
- Prior distribution for the cumulative hazard function

Prior distribution for the survival function

- Assuming survival function is sampled from a Dirichlet process with a parameter function α.
- $\alpha[t,\infty) = cS_0(t)$ where $S_0(t)$ is our prior guess at the survival function and c is a measure on how much weight to put on our prior guess.
- $\alpha(0,\infty) = cS_0(0)$
- Prior mean is given by: $E[S(t)] = \frac{\alpha[t,\infty)}{\alpha[0,\infty)} = \frac{cS_0(t)}{cS_0(0)} = S_0(t)$
- $S_0(t) = \exp(rt)$

The Bayesian nonparametric estimation:

Given the fact that is a conjugate prior the posterior distribution, the parameter α^* is given by:

$$\alpha^*\big((a,b)\big) = \alpha\big((a,b)\big) + \sum_{j=1}^{n} I\left[\delta_j > 0, a < T_j < b\right)$$

n distinct events times

The Bayesian nonparametric estimation:

Assuming M distinct times (censored or uncensored)

The bayes estimator of the survival function is given by:

$$\tilde{S}_D(t) = \frac{\alpha[t,\infty) + Y_{i+1}}{\alpha[0,\infty) + n} \prod_{k=1}^{i} \frac{\alpha[t_k,\infty) + Y_{k+1} + \lambda_k}{\alpha[t_k,\infty)}$$

At time i, Y_i is the number of individuals at risk, and λ_i is the number of censored observations.

For large n the bayes estimator reduces to a Kaplan Meier estimator.

For small sample size the prior will dominate.

How to assess uncertainty?

- How to sample from $\alpha^*\big((a,b)\big)$?

$$\alpha^*\big((a,b)\big) = \alpha\big((a,b)\big) + \sum_{j=1}^{n} I\left[\delta_j > 0, a < T_j < b\right)$$

- The posterior distribution is a Dirichlet

To assess uncertainty (work in progress):

So from Wikipedia we have:

- Using of Gamma-distributed random variables (y_i) one can sample a random vector from Dirichlet distribution

$$Gamma(\alpha_i, 1) = \frac{{y_i}^{\alpha_i - 1} e^{-y_i}}{\Gamma(\alpha_i)}$$

- Then

$$x_i = \frac{y_i}{\sum_{j=1}^{K} y_j}$$

x_i is a sample from a Dirichlet distribution

Take home messages

- In economic evaluations we are interested to assess long term outcomes
- The plausibility of the results should be also considered
- The non-parametric bayesian estimator provides a very natural way to combine two sources of information
- We can decide how much weight we put in our prior knowledge
- This approach is specially useful when patients in the control arm have switch to the experimental arm

References

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- Wikipedia: http://en.wikipedia.org/wiki/Dirichlet_distribution
- Wikipedia: http://en.wikipedia.org/wiki/Melanoma

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