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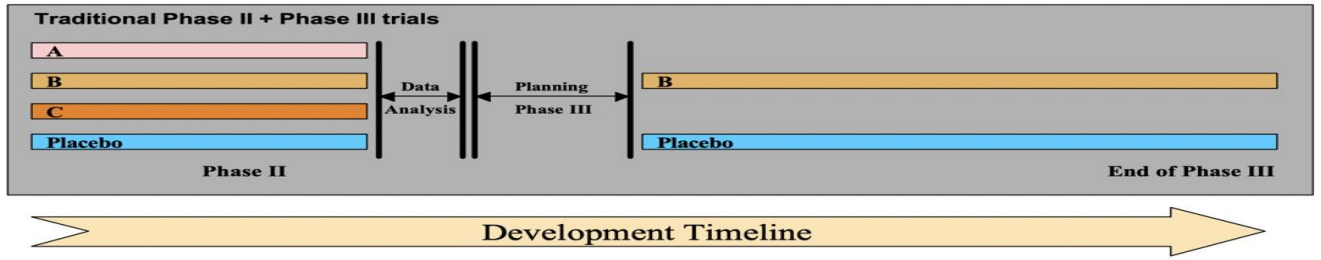
Seamless Bayesian survival designs

Using dichotomized survival data to construct a prior distribution for Bayesian seamless phase II/III designs
Application to Atalante-1 data

Reminder: Seamless Designs



Seamless design

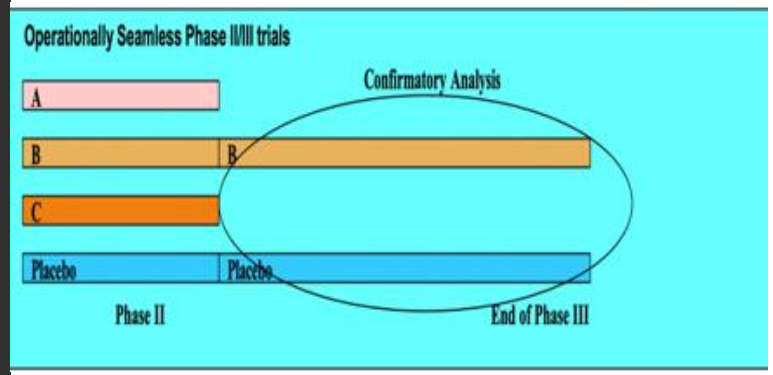
A design that combines into a single trial objectives that are traditionally addressed in separate trials. **Analyses are independent.**

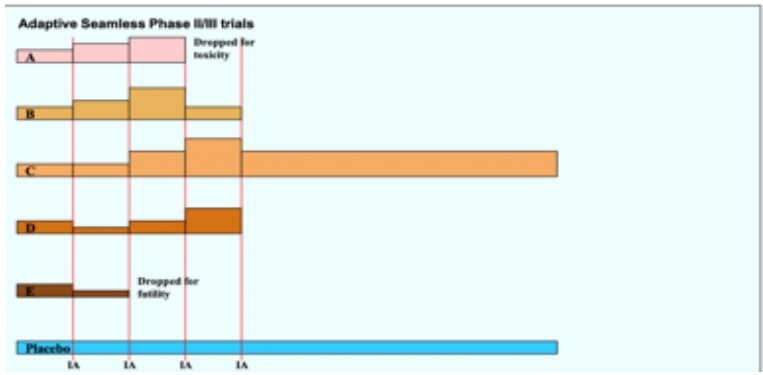
Operationally Seamless

Adaptive Seamless design

A seamless trial in which the final analysis will use **data from patients enrolled before and after** the adaptation.

Inferentially Seamless





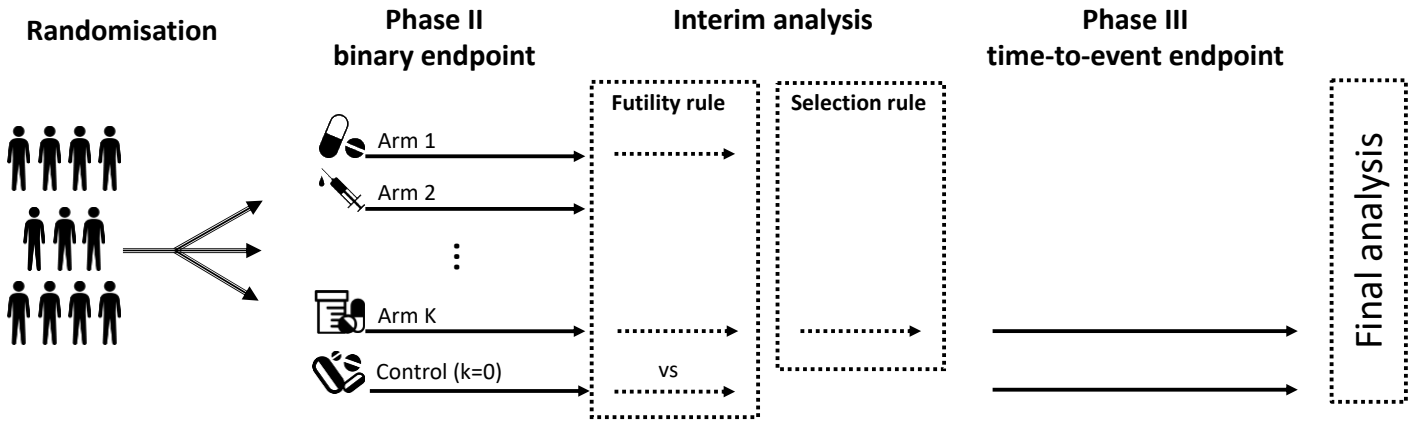
Atalante-1

- ATALANTE study (NCT02654587) from OSE Immunotherapeutics
- RCT comparing the efficacy of OSE2101 (Tedopi) versus the Best Standard of Care in Non-Small-Cell Lung Cancer.
- Operationally Seamless with binary endpoint for the Phase II and overall survival for the Phase III
    - Fleming design for Phase II
    - Log-rank test for Phase III
- Study stopped during Covid-19 pandemic.
- Population of interest (POI) identified during Phase II analyses.
- New phase III study under discussion with EMA/FDA.

Settings

- Bayesian Seamless (Phase II/III) Design with multiple treatment arms.
- Binary endpoint (Survival rate at 12 months) for the first stage and Time to event for the second one (Overall Survival).

- Objective:
  Find the optimal way to transfer information between Phases

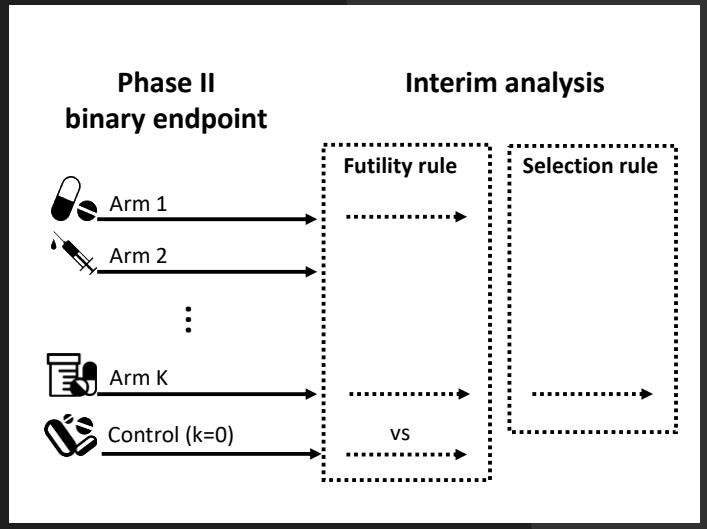


Designs

- 4 Bayesian Designs:
    - Bayesian Inferential (data from all study is used in final Phase III analysis)
    - Bayesian Informative and non-Informative Operational (data from Phase II used for selection and to set prior distribution, then analysis is made with Phase III data only)
    - Non informative Operational Bayesian with Phase II data used in Weibull binary likelihood.

- 1 Frequentist method for comparison:
    - Frequentist Operational seamless with Weibull regression as final test.

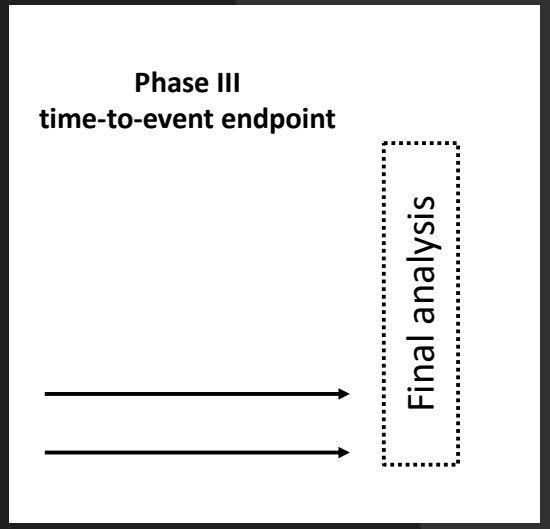
Model and Design Step 1 – Interim Analysis



- K treatment groups simultaneously compared to a common control group (k=0).
- Phase II: for each group we get the number of survivors at one year. $y_{ik}^{*} = 1$ if t > 12 months
  $\sum y_{ik}^{*} \sim Bin(n_k, p_k)$
- $p_k = logit^{-1}(\theta_k)$, with $\theta_k = \theta_0 + \mu_k$
  with $\theta_k \sim N(0,10)$

- Interim analysis: selection of the best arm with posterior predictive probabilities after a threshold futility step
  - Futility: Stop if $P(p_k > p_0) < \tau_1$
  - Selection: $\int p\left(y_{\{i+1,k\}} | p_k\right) \pi_{post}(p_k | y_k) dp_k$

Model and Design Step 2 – Final analysis



- Weibull shape and scale distribution for both group with common shape.
  - $\mathrm{f}(\mathrm{t}|\alpha,\gamma_k) = \frac{\alpha}{\gamma_k}\left(\frac{t}{\gamma_k}\right)^{\alpha-1}\exp(-\left(\frac{t}{\gamma_k}\right)^{\alpha})$
  - Treatment regression covariate introduced with $\beta_k = \log(\gamma_k)$
- Final claim based on $\Delta = \beta_1 - \beta_0$ $\beta_k \sim N(\mu_k, \sigma_k)$, with σ_k being tuned given the design. (i.e., σ_k ~ 1 for non informative and is set up for informative)
- Treatment declared better than control if $\mathrm{P}(\Delta > 0) > 97{,}5\%$

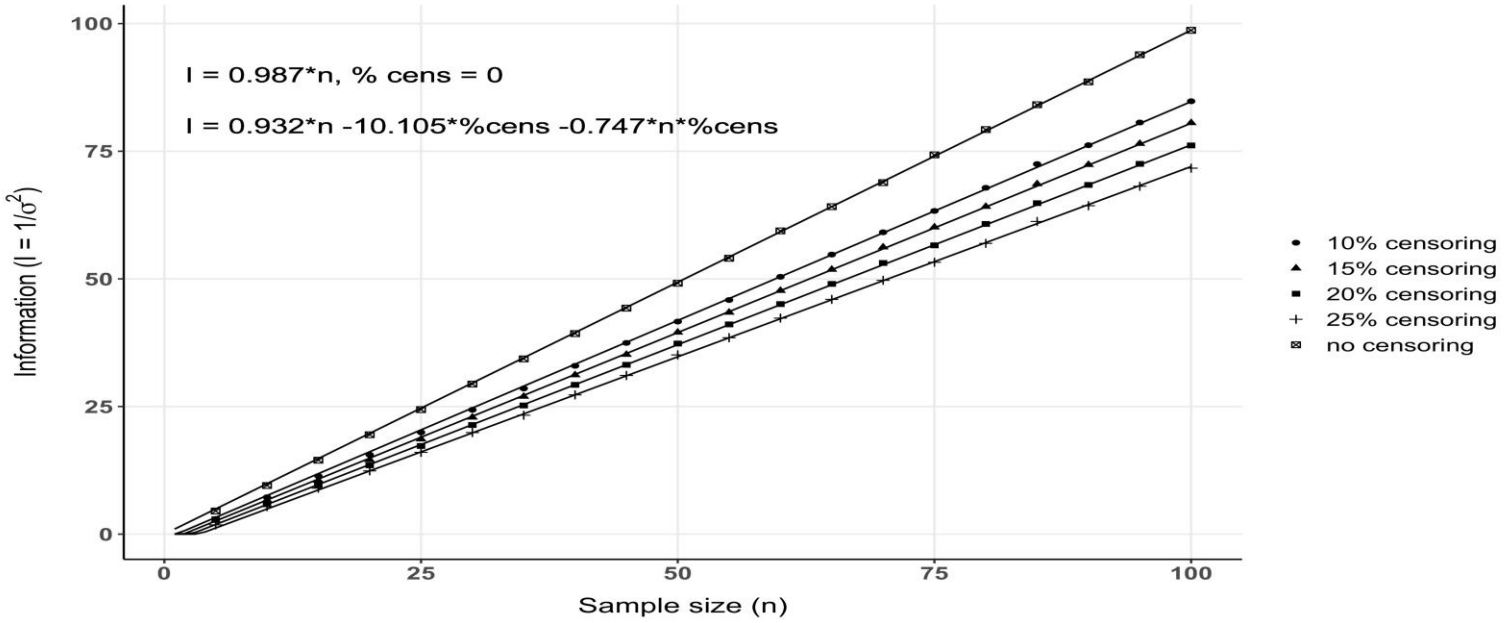
Transfer of Interim information

Two methods:

- To create an informative prior distribution with the data available at Interim, we use $\pi(\beta_k)_{k=0,1} = N(\mu_k, \sigma_k)$

$$\mu_k = \log\left(\frac{-t^*}{\log\left(\tilde{p}_k\right)^{1/\tilde{\alpha}}}\right).$$

- And sigma computed as the graph



The “likelihood approach”

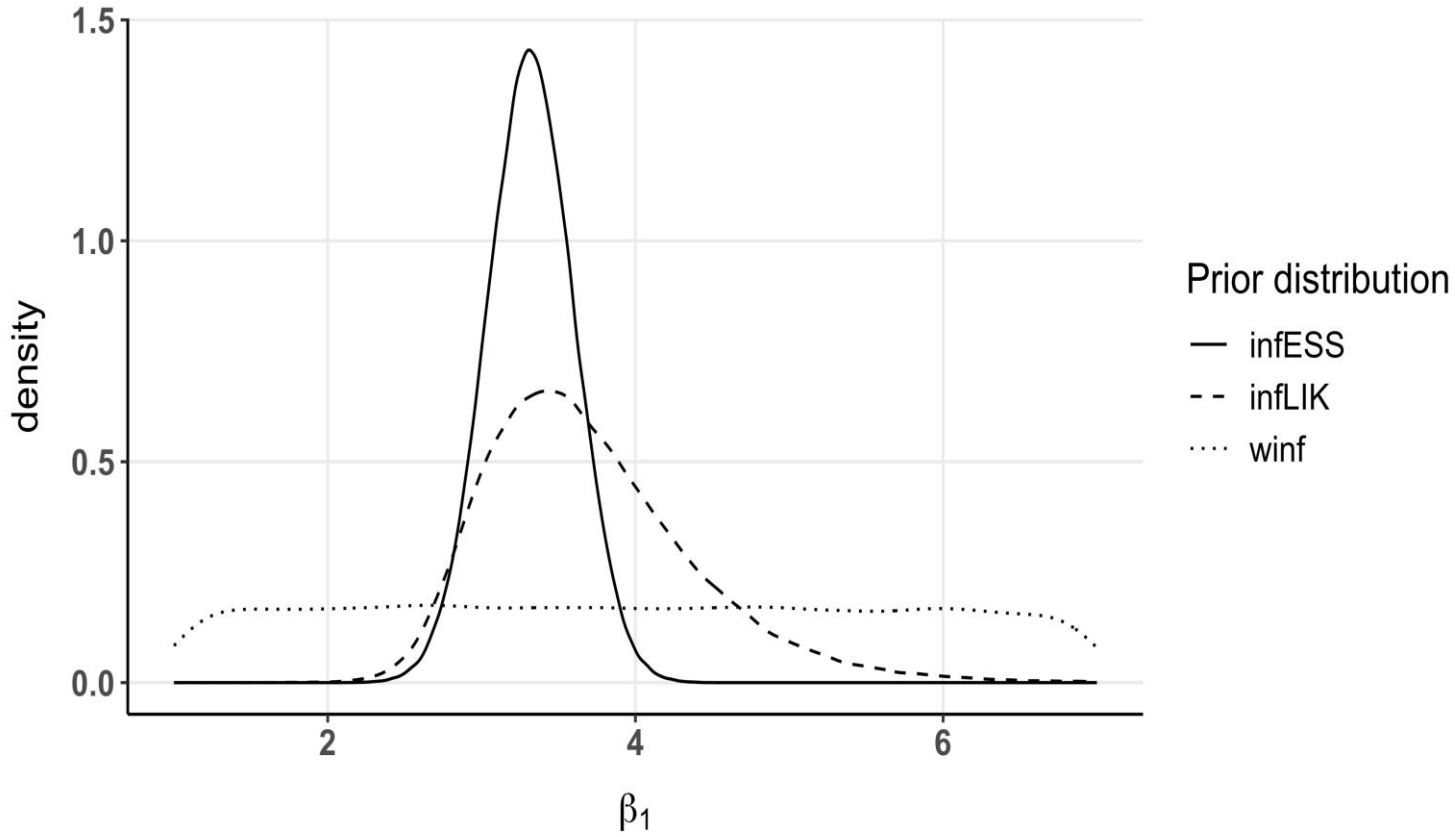
In the second method called the « likelihood » approach, interim information is not transfered through prior distribution of β:

- We use a joint prior distribution for α, β_0, β_1 that is computed using a Weibull binary likelihood

$$\pi(\alpha, \beta_0, \beta_1) \propto \prod_{\tilde{k}=0}^{1} S(t^*|\alpha, \exp(\beta_{\tilde{k}}))^{y_{\tilde{k}}} \left(1 - S(t^*|\alpha, \exp(\beta_{\tilde{k}}))\right)^{n_{\tilde{k}} - y_{\tilde{k}}} \pi(\alpha)\pi(\beta_{\tilde{k}})$$

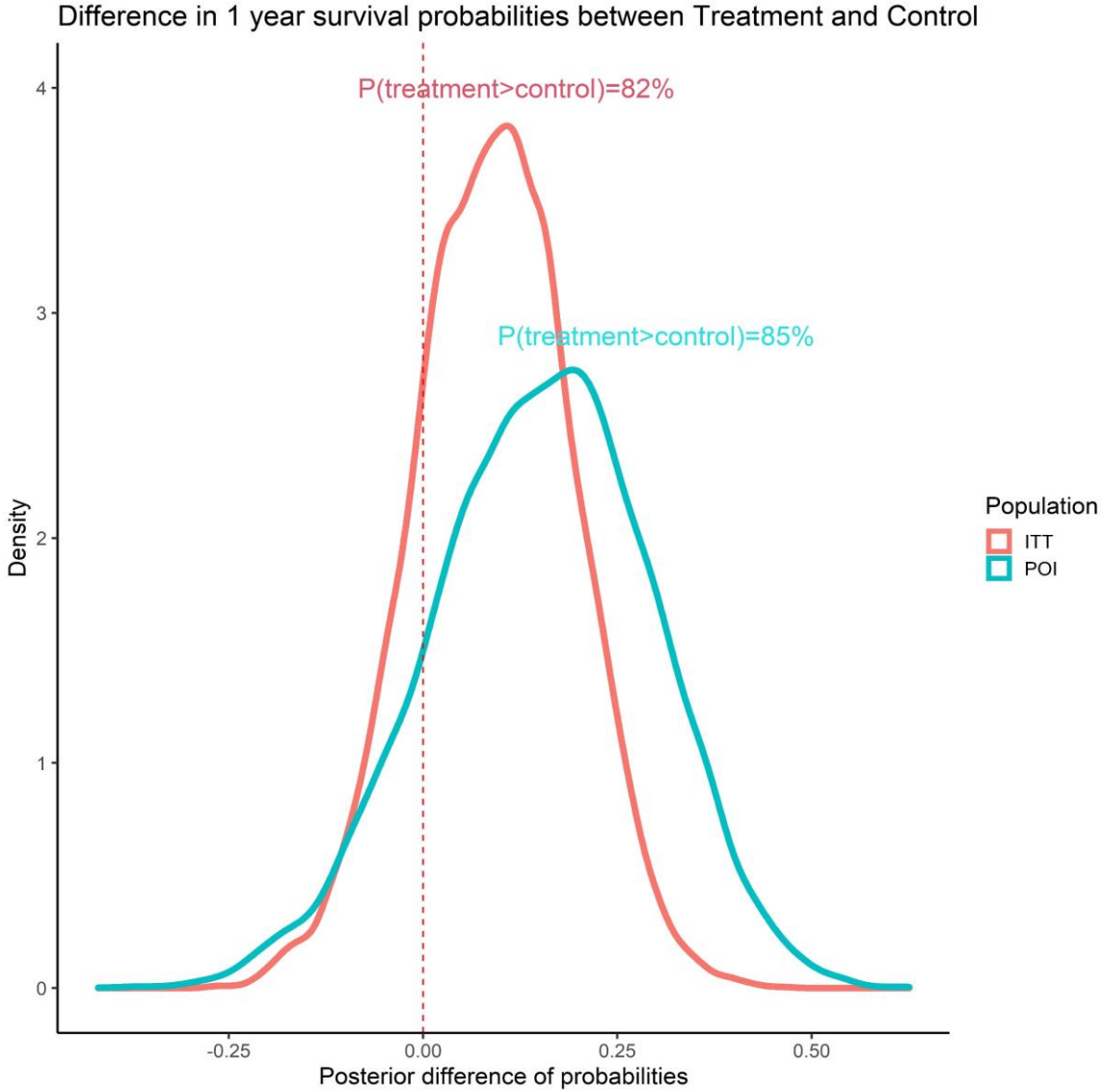
- Marginal prior distributions of α, β_0, β_1 are set non informative

Example of prior distributions obtained



Marginal prior distribution using Phase II data for treatment arm from one simulated study. InfESS is computed with n=17 patients analyzed at Phase II and a censoring rate of 14%

Interim analysis

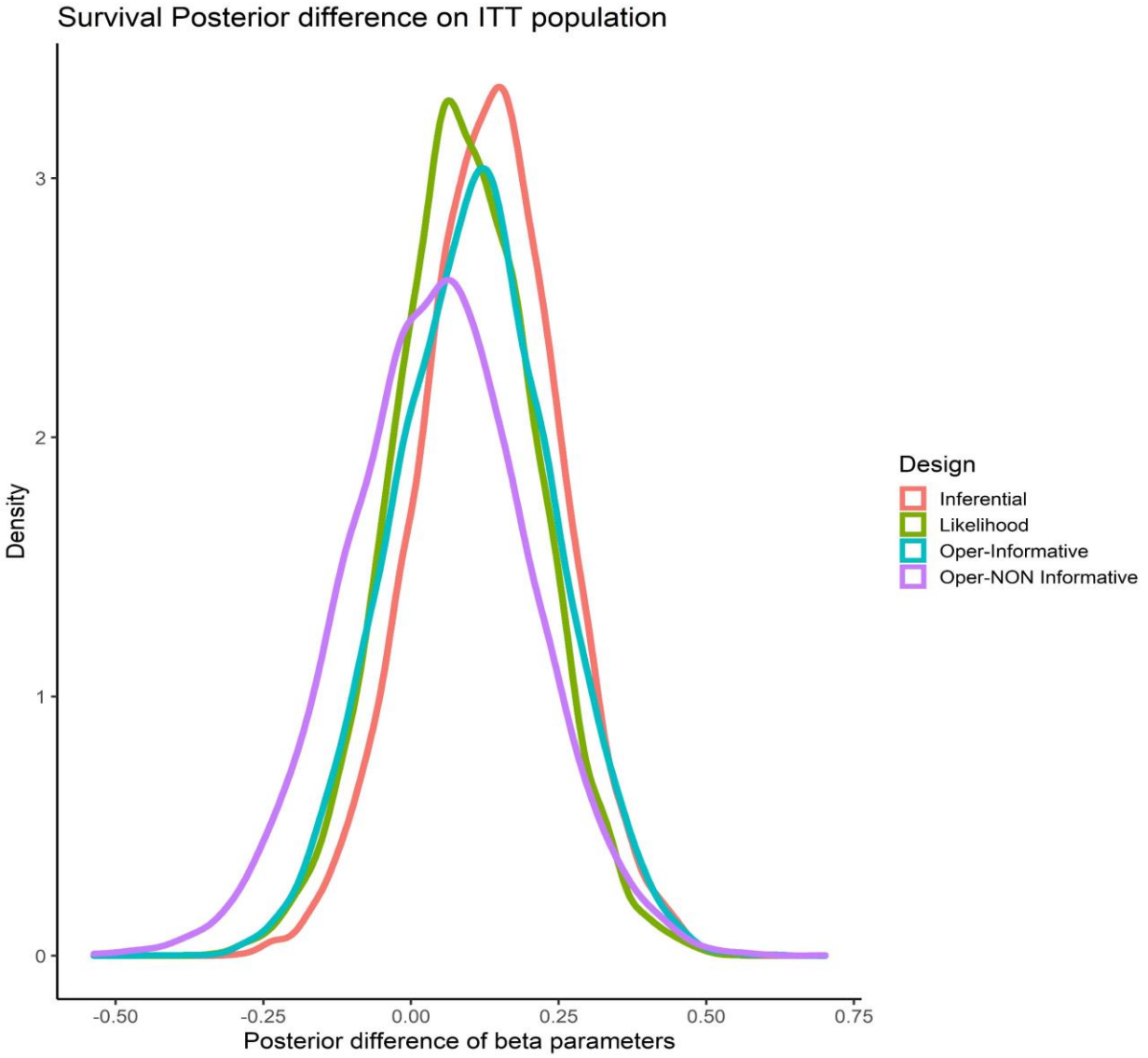


Frequentist Analyses

Design	P(survival control)	P(survival treatment)	Probability Difference
ITT	36%	45%	9%
POI	33%	49%	16%

- P(survival) :
  - Frequentist : observed probability of survival at 1 year (nsurv/n)

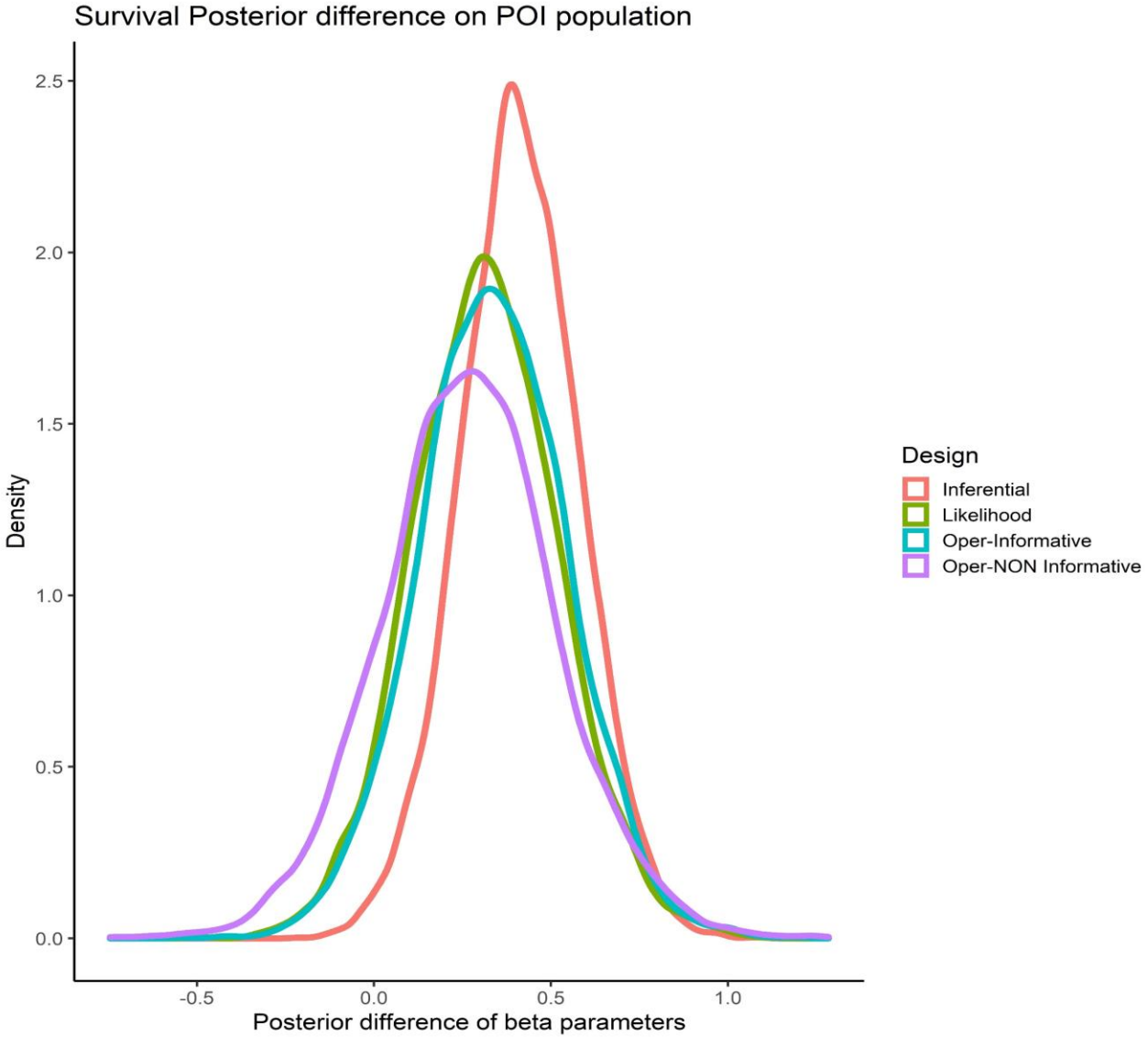
Final Analysis ITT



Design	Mean β0	Mean β1	P(β1-β0>0)
Inferential	2,42	2,55	86%
Likelihood	2,35	2,47	77%
Operational info	2,36	2,47	77%
Operational non info	2,32	2,37	61%

- Operational Frequentist analysis with Weibull regression : p-value = 0,38
- Log-rank test : p = 0.36

Final Analysis POI



Design	Mean β0	Mean β1	P(β1-β0>0)
Inferential	2,30	2,71	99,2%
Likelihood	2,34	2,65	94,3%
Operational info	2,38	2,64	94,8%
Operational non info	2,31	2,57	87%

- Operational Frequentist analysis with Weibull regression: p-value = 0,13
- Inferential Log-rank test: p= 0.017

Discussion

- Atalante-1 confirms results of simulated analyses*
- Bayesian analyses allows to use more information, but type I error must be checked (simulation study).
- Extension of the method to subpopulation analysis.
- Using Bayesian statistics in primary analyses is challenging during scientific advices discussions.

*Using dichotomized survival data to construct a prior distribution for Bayesian seamless phase II/III designs Submitted in June 22.